





Use of the Accelerate Pheno System for Identification and Antimicrobial Susceptibility Testing of Pathogens in Positive Blood Cultures and Impact on Time to Results and Workflow

Angella Charnot-Katsikas,^a  Vera Tesic,^a Nedra Love,^a Brandy Hill,^a Cindy Bethel,^a Sue Boonlayangoor,^a  Kathleen G. Beavis^a

^aClinical Microbiology Laboratory, Department of Pathology, University of Chicago Medicine, Chicago, Illinois, USA

ABSTRACT The Accelerate Pheno system uses automated fluorescence *in situ* hybridization technology with morphokinetic cellular analysis to provide rapid species identification (ID) and antimicrobial susceptibility testing (AST) results for the most commonly identified organisms in bloodstream infections. The objective was to evaluate the accuracy and workflow of bacterial and yeast ID and bacterial AST using the Accelerate Pheno system in the clinical microbiology laboratory. The consecutive fresh blood cultures received in the laboratory were analyzed by the Accelerate Pheno system within 0 to 8 h of growth detection. ID/AST performance, the average times to results, and workflow were compared to those of the routine standard of care. Of the 232 blood cultures evaluated (223 monomicrobial and 9 polymicrobial) comprising 241 organisms, the overall sensitivity and specificity for the identification of organisms were 95.6% and 99.5%, respectively. For antimicrobial susceptibility, the overall essential agreement was 95.1% and categorical agreement was 95.5% compared to routine methods. There was one very major error and 3 major errors. The time to identification and the time to susceptibility using the Accelerate Pheno system were decreased by 23.47 and 41.86 h, respectively, compared to those for the standard of care. The reduction in hands on time was 25.5 min per culture. The Accelerate Pheno system provides rapid and accurate ID/AST results for most of the organisms found routinely in blood cultures. It is easy to use, reduces hands on time for ID/AST of common blood pathogens, and enables clinically actionable results to be released much earlier than with the current standard of care.

KEYWORDS Accelerate, blood culture, identification, susceptibility, turnaround time, workflow

Up to one in four patients with sepsis die from organ failure caused by the hosts' immune responses to infection. Blood cultures need to be collected before antimicrobials are administered, and rapid identification and susceptibility of causative organisms can aid in the lifesaving administration of targeted antimicrobial therapy (1, 2). Routine methods of microbial identification and susceptibility testing might require 24 to 48 h, delaying the use of targeted therapy and timely de-escalation (3, 4). Studies have shown that a delayed administration of antibiotics to septic patients is associated with increased mortality among adults and neonates (5, 6). Also, the initial empirical therapy can be inappropriate in up to 50% of cases (7, 8). This delay leads to increased patient morbidity, mortality, length of stay (LOS), and cost of care (9, 10).

The current standard of care (SOC) for the diagnosis of bloodstream infections (whether or not the patient presents with sepsis) includes blood cultures. Advances are needed to decrease the turnaround time (TAT) for the diagnosis of bloodstream infections. After the organisms multiply and the blood culture is flagged positive, many

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Address correspondence to Vera Tesic, vtesic@bsd.uchicago.edu. A.C.-K. and V.T. contributed equally to this article.

different platforms are available for the rapid identification of pathogens. Methods such as matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (11), fluorescence *in situ* hybridization with peptide nucleic acid probes (PNA-FISH) (12), multiplex PCR (13), and multiplex PCR coupled to electrospray ionization mass spectrometry (PCR/ESI-MS) (14) are rapid, and some have the ability to identify genetic antimicrobial resistance determinants, but none produce a full phenotypic susceptibility result. These methods have a clinical impact if the reporting is coupled with antimicrobial stewardship intervention (3, 15). A recent assessment of physicians' interpretations of rapid blood culture identification and antibiotic prescribing practices in a single medical center concluded that the use is suboptimal and the misinterpretation of results can be at rates of up to 50% (16). Some of the PCR-based methods can detect pathogens directly from the blood sample rather than from a positive culture, providing faster identification (17); an accompanying blood culture and isolate are necessary for susceptibility results.

We sought to evaluate the ability of the Accelerate Pheno system (AXDX) to identify bloodstream isolates and perform susceptibility testing. The system uses a fully automated fluorescence *in situ* hybridization (FISH) technology for a rapid genomic identification of the most common pathogens causing bloodstream infections (BSI). Each of the 16 FISH identification (ID) probe cocktails employs a proprietary combination of universal and species-specific probes for species- or in some cases genus-level identification and also supports a unique “monomicrobial call,” indicating that only one pathogen is present (18). Following an identification, the system uses morphokinetic cellular analysis for phenotypic antimicrobial susceptibility testing (AST). For each drug-specific AST, a single concentration of antibiotic is used to provide MICs and categorical interpretations (susceptible [S], intermediate [I], or resistant [R]) based on FDA and/or CLSI breakpoints (19). The Accelerate Pheno system combines ID and AST in one instrument producing an ID within 90 min and AST in approximately 7 h from a positive blood culture specimen, giving the physician timely guidance to escalate or de-escalate empirical therapy and optimize definitive therapy.

MATERIALS AND METHODS

Blood cultures collected from March 2016 to October 2016 at the University of Chicago Medicine were included in the study. The cultures were collected in Bactec Plus aerobic/F medium, Bactec Plus anaerobic/F medium or Bactec Peds Plus/F medium bottles (Becton, Dickinson, Baltimore, MD) and incubated in a Bactec FX continuous blood culture monitoring instrument (Becton, Dickinson, Baltimore, MD) until growth was detected. The time of growth detection was recorded. Positive blood culture specimens (5 ml) were tested fresh within 8 h of growth detection on an early version (pre-FDA clearance) of the Accelerate Pheno system (v1.0 software) with the Accelerate PhenoTest BC kit as per the manufacturer's instructions. Only the first positive blood culture (aerobic or anaerobic) per patient within 28 days was included in the study. Known off-panel organisms such as Gram-positive rods were excluded from the study. The start times of the runs and times when identification (ID) and AST results became available on the Accelerate Pheno system were recorded. At the same time, positive blood culture samples were processed using routine methods as per the SOC, using the Vitek MS system (bioMérieux, Durham, NC), Vitek 2 system (bioMérieux, Durham, NC), or biochemical assays (including catalase, pyrrolidonyl arylamidase [PYR], Remel; Thermo Fisher Scientific, Lenexa, KS, USA) and BactiStaph (Remel; Thermo Fisher Scientific, Lenexa, KS, USA) for identification. For antimicrobial susceptibility testing (AST), the comparator for most combinations was the Vitek 2 system using the AST-GN75 card for Gram-negative organisms and AST-GP67 for staphylococci and enterococci (bioMérieux, Durham, NC). However, the Etest (bioMérieux, Durham, NC) was the comparator for colistin, and disk diffusion (Becton Dickinson Microbiology Systems, Sparks, MD) was the comparator for testing *Acinetobacter baumannii* with amikacin, ampicillin-sulbactam, cefepime, ciprofloxacin, meropenem, and piperacillin-tazobactam. Moreover, for the *Enterobacteriaceae*, colistin was only tested against meropenem-resistant organisms.

Frozen blood aliquots were also prepared at this time to accurately capture the organisms present at the time the positive bottle was loaded on the Accelerate Pheno system. In addition, isolates were frozen at -70°C for discrepancy analysis.

The times when identification and AST results were available were recorded.

Research use only (RUO) organism-antimicrobial combinations were evaluated for research purposes only and are not for use in diagnostic procedures. The exclusion criteria included the following: indeterminate results, samples run >8 h after growth detection, samples for which the Accelerate Pheno system detected 4 or more organisms or AST results that were reported for 2 organisms in a sample.

This study was approved by institutional review board (IRB) under study number IRB14-1358.

Data analysis. (i) Identification and antimicrobial susceptibility. The following Gram-positive and Gram-negative organisms and yeasts were included in the ID comparative analysis: *Staphylococcus*

aureus, *Staphylococcus lugdunensis*, coagulase-negative staphylococci (i.e., *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Staphylococcus capitis*, *Staphylococcus lugdunensis*, and *Staphylococcus warneri* [not differentiated]), *Enterococcus faecium*, *Enterococcus faecalis*, *Streptococcus* spp. (i.e., *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus gallolyticus*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae* [not differentiated]), *Escherichia coli*, *Klebsiella* spp. (i.e., *Klebsiella pneumoniae* and *Klebsiella oxytoca* [not differentiated]), *Enterobacter* spp. (i.e., *Enterobacter cloacae* and *Enterobacter aerogenes* [not differentiated]), *Proteus* spp. (i.e., *Proteus mirabilis* and *Proteus vulgaris* [not differentiated]), *Citrobacter* spp. (i.e., *Citrobacter freundii* and *Citrobacter koseri* [not differentiated]), *Serratia marcescens*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Candida glabrata*.

AST was performed using the following antimicrobials for the Gram-positive organisms: ampicillin, erythromycin, linezolid, trimethoprim-sulfamethoxazole, and vancomycin. Cefoxitin was also tested against *S. aureus* and the coagulase-negative staphylococci to detect methicillin resistance. For the Gram-negative organisms, the following were tested: amikacin, ampicillin-sulbactam, cefazolin, cefepime, ceftazidime, ceftriaxone, ciprofloxacin, colistin, ertapenem, gentamicin, meropenem, piperacillin-tazobactam, and tobramycin. For any sample with >1 strain of the same species, a single composite SOC AST profile was created using the most resistant MIC result for each drug tested and was used as the reference for analysis.

The SOC results were used as the reference comparator for bacterial identification and AST. Results were interpreted according to the CLSI 2016 M100-S26 for all antimicrobials with the exception of colistin, which was interpreted according to EUCAST 2016 standards for the *Enterobacteriaceae*.

To determine the identification accuracy, the sensitivity and specificity were calculated by using the FISH ID probe for the AXDX and the results were compared to those of the SOC: sensitivity = $(100 \times TP)/(TP + FN)$; specificity = $(100 \times TN)/(TN + FP)$, where TP is the true positive, FN is the false negative, TN is the true negative, and FP is the false positive.

For AST accuracy, essential agreement (EA), categorical agreement (CA), very major error (VME), major error (ME), and minor error (MiE) rates were calculated as applicable using AXDX results compared to those of the SOC for each antimicrobial tested. EA is the percentage of the total test results within one doubling dilution of the reference result. CA is the percentage of the total test results with the same categorical interpretation result as the reference result. VME is the percentage of the resistant isolates by the SOC that tested susceptible by the AXDX. ME is the percentage of the susceptible isolates by the SOC that tested resistant by the AXDX. MiE is the percentage of the total test results in which one result (from the AXDX or the SOC) is intermediate and the other is not. For resistance phenotype tests, only categorical agreement and VME and ME rates were calculated.

(ii) Discrepancy analysis. Discrepancy testing was performed for isolates that did not show agreement between the AXDX and the SOC. Samples were plated on tryptic soy agar plates containing 5% sheep's blood and incubated at 35°C for 18 to 24 h. For frozen blood aliquots, MacConkey agar and Columbia colistin-nalidixic acid (CNA) agar containing 5% sheep's blood were also used to differentiate possible mixed sample types. Observations were made after the initial 18 to 24 h of growth to ensure purity. For mixed cultures, each morphology was isolated on blood agar plates and incubated at 35°C for 18 to 24 h. Original plates and isolated morphologies were stored at 4°C, and fresh subcultures were made from these master plates for either identification or antimicrobial susceptibility testing needs.

Frozen blood aliquots previously prepared were used for discrepant ID testing. This ensured that organisms were captured and preserved in their present state at the time the blood aliquots were originally tested. Observations of colony morphologies and Gram stains were recorded for each sample. For organisms identified by the AXDX but not by the SOC, if the organism was not detected by Gram stain and/or culture, the isolate was considered a false positive. For organisms identified by the SOC but not by the AXDX, if the organism was detected by Gram stain or culture, the isolate was considered a false negative. The organisms present in the culture were identified using a third-party comparator automated Vitek 2 system for Gram-positive, Gram-negative, and yeast identification (ID cards no. GP 21342, GN 21341, and YST 21343) according to the procedures recommended for the Vitek 2 system. If the original AXDX result matched the third-party result, the result was resolved to be a true positive. If the third-party result matched the SOC result, the error was adjudicated toward the SOC. Vitek 2 was considered a third-party comparator, because Vitek 2 was not used to obtain the original SOC ID result for any of the samples that underwent ID discrepancy testing.

Any samples with a VME/ME or select MiE or EA errors (only for drugs with overall EA <90%) were included in AST discrepancy testing. For AST discrepancy testing, previously frozen isolates from pure culture were used. The growth characteristics and purity were recorded after 24 h of incubation. Cultures were passaged twice on medium before being tested in triplicates via the CLSI standardized broth microdilution method (BMD) (20), herein referred to as the "reference method." The modal BMD result was used as the reference. If there was no mode, the BMD was repeated and the modal BMD from the resulting 6 tests was used as the reference. For resistance screening, the isolates were subcultured twice before Kirby-Bauer disk diffusion (cefoxitin) or triplicate BMD for inducible clindamycin resistance was performed. In cases where the reference method disagreed with both the AXDX and the SOC, the reference method was used as the true result. SOC testing was not repeated for discrepancy analysis.

(iii) Workflow. A workflow analysis was performed by Lynnova Consulting. The workflows for the Accelerate Pheno system and for SOC identification, antimicrobial susceptibility testing, and quality control methods were analyzed and compared on the basis of the average time to process samples observed during a 30-h period.

TABLE 1 Discrepant results in organism identification

Organism	No. of false positives				No. of false negatives			
	Total	Resolved to AXDX	Resolved to SOC	Unresolved	Total	Resolved to AXDX	Resolved to SOC	Unresolved
Gram positives								
Coagulase-negative <i>Staphylococcus</i> spp.	3	0	3	0	1	1 ^b	0	0
<i>E. faecalis</i>	— ^a	—	—	—	2	0	2 ^c	0
<i>E. faecium</i>	—	—	—	—	2	0	2	0
<i>S. aureus</i>	2	0	2	0	1	0	1	0
<i>S. lugdunensis</i>	—	—	—	—	—	—	—	—
<i>Streptococcus</i> spp.	6	1	4 ^d	1	—	—	—	—
Gram negatives								
<i>A. baumannii</i>	—	—	—	—	—	—	—	—
<i>Citrobacter</i> spp.	—	—	—	—	—	—	—	—
<i>Enterobacter</i> spp.	1	0	1	0	3	1 ^e	2	0
<i>E. coli</i>	—	—	—	—	1	0	1 ^f	0
<i>Klebsiella</i> spp.	—	—	—	—	2	1 ^g	1	0
<i>Proteus</i> spp.	—	—	—	—	—	—	—	—
<i>P. aeruginosa</i>	—	—	—	—	—	—	—	—
<i>S. marcescens</i>	—	—	—	—	—	—	—	—
Yeast								
<i>C. albicans</i>	—	—	—	—	—	—	—	—
<i>C. glabrata</i>	5	0	5	0	—	—	—	—
Total	17	1	15	1	12	3	9	0

^a—, no discrepant results occurred.

^bFalse-negative coagulase-negative *Staphylococcus* spp. occurred in a polymicrobial sample also containing *Acinetobacter haemolyticus* according to the SOC.

^cOne false-negative *E. faecalis* occurred in a polymicrobial sample also containing *E. coli* according to the SOC.

^dFalse-positive *Streptococcus* spp. (*S. salivarius*) occurred in a polymicrobial sample also containing *E. coli* according to the SOC.

^eFalse-negative *Enterobacter* spp. (*E. cloacae*) occurred in a polymicrobial sample also containing *Acinetobacter jejunii* and *A. baumannii* according to the SOC.

^fFalse-negative *E. coli* occurred in a polymicrobial sample also containing *K. pneumoniae* according to the SOC.

^gFalse-negative *Klebsiella* spp. (*K. pneumoniae*) occurred in a polymicrobial sample also containing *E. cloacae* according to the SOC.

RESULTS

Identification. Of the 296 blood cultures, 64 were excluded from further analysis due to technical failures ($n = 4$), invalid (non-report of) ID results ($n = 30$), a time lapse of more than 8 h after positivity of the blood culture ($n = 13$), or the failure to meet study inclusion criteria (i.e., a duplicate patient sample or a sample that was not a blood culture) ($n = 17$). Final results were obtained for the remaining 232 (221 monomicrobial and 11 polymicrobial) blood cultures comprising 244 (214 on-panel and 30 off-panel) organisms. After adjudication, there were 223 monomicrobial and 9 polymicrobial blood cultures with 241 (212 on-panel and 29 off-panel) organisms detected; of the 212 on-panel organisms, 8 indeterminate results were excluded from the analysis. Of the remaining 204 on-panel results, 195 (95.6%) were identified correctly by the AXDX.

Table 1 shows the discrepant results in organism identification. There were a total of 28 cultures with 29 discrepancies in identification that required further evaluation: 17 initial false positives (FPs) and 12 initial false negatives (FNs) (Table 1). Six of these involved polymicrobial cultures for which the two systems disagreed on one of the organism identifications in the group. Four (14%) of the discrepancies were resolved to agree with results of the AXDX, leaving 16 FPs and 9 FNs in the postadjudicated data set.

Notably, all 5 FP *Streptococcus* species had genus-level agreements with the reference method. Of the 16 remaining FP results, 5 involved *Streptococcus* species (*S. constellatus*, *S. dysgalactiae*, *S. anginosus*, *S. pyogenes*, and *S. salivarius*) that had genus-level agreement but are not claimed at the species level on the Accelerate PhenoTest BC kit; the remainder included coagulase-negative staphylococci (3), *S. aureus* (2), *Enterobacter* spp. (1), and *C. glabrata* (5). Eight of these were mitigated by comparing to the Gram stain result, which did not indicate the presence of the false-positive organism. All 5 *C. glabrata* isolates tested were determined to be FPs. Per specimen

TABLE 2 Performance characteristics of the Accelerate Pheno system for organism identification (after adjudication of discrepant results)

Organism	Sensitivity ^a		Specificity ^b	
	No. detected/ no. tested	%	No. detected/ no. tested	%
Gram positives				
Coagulase-negative <i>Staphylococcus</i> spp.	52/52	100	169/172	98.3
<i>Enterococcus faecalis</i>	15/17	88.2	215/215	100
<i>Enterococcus faecium</i>	3/5	60	227/227	100
<i>Staphylococcus aureus</i>	18/19	94.7	200/202	99
<i>Staphylococcus lugdunensis</i>	0/0	NA ^c	228/228	100
<i>Streptococcus</i> spp.	21/21	100	205/210	97.6
Total	109/114	95.6	1,244/1,254	99.1
Gram negatives				
<i>Acinetobacter baumannii</i>	3/3	100	229/229	100
<i>Citrobacter</i> spp.	2/2	100	230/230	100
<i>Enterobacter</i> spp.	11/13	84.6	215/216	99.5
<i>Escherichia coli</i>	30/31	96.8	201/201	100
<i>Klebsiella</i> spp.	20/21	95.2	211/211	100
<i>Proteus</i> spp.	3/3	100	229/229	100
<i>Pseudomonas aeruginosa</i>	9/9	100	223/223	100
<i>Serratia marcescens</i>	3/3	100	229/229	100
Total	81/85	95.3	1,767/1,768	99.9
Yeast				
<i>Candida albicans</i>	2/2	100	229/229	100
<i>Candida glabrata</i>	3/3	100	224/229	97.8
Total	5/5	100	453/458	98.9
Overall^d	195/204	95.6	3,464/3,480	99.5

^aEight indeterminate results were excluded from sensitivity calculations. Sensitivity calculations considering on-panel organisms only were identical.

^bTwenty indeterminate results were excluded from specificity calculations. The total specificity calculations considering on-panel organisms only were as follows: Gram positives, 1,090/1,095 (99.5%); Gram negatives, 1,552/1,552 (100%); yeast, 399/404 (98.8%); and overall, 3,041/3,051 (99.7%).

^cNA, not applicable.

^dTotal overall genus-level agreement for all probes was 91.4%.

($n = 232$), the overall FP rate was 6.9%; the FP rates for Gram-positive, Gram-negative, and yeast organisms were 4.3%, 0.4%, and 2.2%, respectively. However, there were 16 FISH ID probe results per specimen. Per FISH ID probe result ($n = 3,712$), the overall FP rate was 0.4%; the FP rates for Gram-positive, Gram-negative, and yeast organisms were 0.3%, 0.03%, and 0.1%, respectively.

The 9 remaining FN results included *E. faecalis* (2), *E. faecium* (2), *S. aureus* (1), *Enterobacter* spp. (2), *E. coli* (1), and *Klebsiella* spp. (1). Eight of the 9 FNs were mitigated; one of these was a polymicrobial by the SOC method that was mitigated by comparing to the Gram stain result, which indicated an additional organism was present, and five more would likely be mitigated through additional testing as they were negative for the monomicrobial call. As a result, an expert rule would print the following note on the lab report. "Recommend culture due to possibility of another organism being present." In other words, the system is indicating an organism is present that was not identified by the on-panel ID probes. The two FN *Enterobacter* spp. tested positive on the retests with updated software v1.2, which includes improved algorithms for *Enterobacter* spp. detection not available in software v1.0. Per specimen ($n = 232$), the overall FN rate was 3.9%; the FN rates for Gram-positive and Gram-negative organisms were 2.2% and 1.7%, respectively. Per FISH ID probe result ($n = 3,712$), the overall FN rate was 0.2%; the FN rates for Gram-positive and Gram-negative organisms were both 0.1%. There were no FNs for yeast.

Table 2 denotes the ID performance characteristics of the Accelerate Pheno system for both on-panel and off-panel isolates following adjudication. The sensitivity and specificity for bacterial identification were 95.6% and 99.1% (Gram positives), 95.3% and

TABLE 3 Summary of very major and major errors in antimicrobial susceptibility

Antibiotic	No. of VMEs ^a					No. of MEs ^b				
	Total	Resolved to AXDX	Resolved to SOC	Resolved to neither	Unresolved	Total	Resolved to AXDX	Resolved to SOC	Resolved to neither	Unresolved
Gram-positive organisms										
Erythromycin	2	2	0	0	0	0	0	0	0	0
Linezolid	1	1	0	0	0	0	0	0	0	0
Gram-negative organisms										
Ampicillin-sulbactam	1	0	0	1	0	0	0	0	0	0
Cefepime	0	0	0	0	0	1	0	0	1	0
Ceftazidime	1	0	0	1	0	1	0	1	0	0
Ciprofloxacin	1	1	0	0	0	0	0	0	0	0
Ertapenem	1	0	0	1	0	1	0	1	0	0
Resistance phenotype tests										
Cefoxitin (methicillin resistance)	1	0	1	0	0	1	1	0	0	0
Total	8	4	1	3	0	4	1	2	1	0

^aVME, very major error.^bME, major error.

99.9% (Gram negatives), and 100% and 98.9% (yeast), respectively. The overall sensitivity and specificity were 95.6% and 99.5%, respectively. The total overall sensitivity and specificity calculations considering on-panel organisms only were 95.6% and 99.7%, respectively.

The *Streptococcus* genus probe is claimed to detect *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus gallolyticus*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae* (not differentiated). However, the probe also detected other *Streptococcus* species that are not claimed for the Accelerate Pheno system. The agreement on a genus level was 100% for the streptococci. The other genus probes showed high performance except for *Enterobacter*; genus-level performance for this probe was 78.6%.

Antimicrobial susceptibility. Antimicrobial susceptibility results were produced for 151 isolates with a total of 944 (236 Gram-positive and 708 Gram-negative) organism-antimicrobial test results. Thirty-seven (15.7%) of the Gram-positive and 75 (10.6%) of the Gram-negative results were resistant to one or more antimicrobials.

There were 33 samples with 33 discrepancies requiring discrepancy resolution for AST and/or resistance phenotype detection. There were initially 8 VMEs, 4 MEs, and 21 MiEs. Table 3 lists the summary of VME and ME discrepancy testing results, and Tables 4, 5, and 6 provide the AST performance results obtained by antibiotic and organism groups. Three of the VMEs involved Gram-positive organisms tested against erythromycin (2) and linezolid (1); four involved Gram-negative organisms tested against ampicillin-sulbactam (1), ceftazidime (1), ciprofloxacin (1), and ertapenem (1); one involved cefoxitin resistance testing for methicillin-resistant coagulase-negative *Staphylococcus* (MRS) spp. Four of the VMEs were resolved to agree with the AXDX results, and one was resolved to agree with the SOC result. The remaining 3 were not resolved with either system (i.e., they repeatedly tested as “intermediate” by the reference method), resulting in those VMEs being reclassified as MiEs. Therefore, in the final analysis, there was one VME for cefoxitin and coagulase-negative *Staphylococcus* spp., resulting in an overall VME rate of 0.7%.

The 4 MEs involved Gram-negative organisms tested against cefepime (1), ceftazidime (1), and ertapenem (1); one involved cefoxitin resistance testing for methicillin-resistant coagulase-negative *Staphylococcus* (MRS) spp. One ME was resolved to agree with the AXDX result, 2 resolved with the SOC results, and 1 was resolved with neither, yielding that ME to be reclassified as an MiE according to the reference AST method.

There were initially 43 minor errors, 40 involving Gram-negative and 3 involving Gram-positive organisms. Thirty-six (83.7% of MiEs) specifically involved the *Enterobac-*

TABLE 4 Performance characteristics of the Accelerate Pheno system for Gram-positive AST performance by antibiotic and organism grouping^a

Antibiotic	EA		CA		No. of results					
	No. results/total ^b	%	No. results/total ^c	%	VME	ME	MiE	S	I	R
<i>Staphylococcus aureus</i>										
Erythromycin	16/17	94.1	16/17	94.1	0	0	1	9	1	7
Linezolid	17/17	100	17/17	100	0	0	0	17	0	0
Trimethoprim-sulfamethoxazole ^d	17/17	100	17/17	100	0	0	0	16	0	0
Vancomycin	16/17	94.1	17/17	100	0	0	0	17	0	0
Total	66/68	97.1	67/68	98.5	0	0	1	59	1	7
Coagulase-negative <i>Staphylococcus</i> spp.										
Erythromycin ^d	44/45	97.8	44/45	97.8	0	0	1	18	0	27
Linezolid ^d	46/47	97.9	47/47	100	0	0	0	47	0	0
Vancomycin	44/46	95.7	46/46	100	0	0	0	46	0	0
Total	134/138	97.1	137/138	99.3	0	0	1	111	0	27
<i>Enterococcus</i> spp.										
Ampicillin	8/8	100	8/8	100	0	0	0	7	0	1
Linezolid	8/8	100	8/8	100	0	0	0	8	0	0
Vancomycin	13/14	93	13/14	93	0	0	1	12	0	2
Total	29/30	96.7	29/30	96.7	0	0	1	27	0	3
Overall	229/236	97	233/236	98.7	0	0	3	197	1	37

^aResults based on CLSI 2016 breakpoints.

^bValues are the numbers of results within one doubling dilution of the reference results over the total numbers of test results.

^cValues are the numbers of results with same categorical interpretation as the reference results over the total numbers of test results.

^dIncludes data from one or more organism/antimicrobial combinations that are research use only (RUO) and not for use in diagnostic procedures.

teriacae. Twenty-one fulfilled criteria for further discrepancy resolution. Five were resolved in favor of the AXDX and 10 in favor of the SOC. The remaining 6 MiEs either remained unresolved ($n = 5$) due to the lack of a BMD mode or nonviable organisms or were resolved to neither AXDX nor SOC results ($n = 1$), i.e., if the AXDX result was intermediate, the SOC result was susceptible and the discrepant test result was resistant.

One ampicillin-sulbactam minor error was reclassified as an ME according to the reference AST method. Therefore, in the final analysis, there were 3 MEs and 41 MiEs, resulting in an overall ME rate of 0.4% (Tables 4 to 6).

EA was obtained in 95.1% and CA in 95.5% of results. For the Gram-positive organisms, EA and CA were 97% and 98.7%, respectively (Table 4). For the Gram-negative organisms, EA and CA were 94.4% and 94.2%, respectively (Table 5).

The EAs and CAs ranged from 93% to 100% for the Gram-positive organisms; the results obtained for all antimicrobials were >90% (Table 4). For the *Enterobacteriaceae*, the EAs ranged from 83.8% (ampicillin-sulbactam) to 100% and CAs ranged from 81.1% (ampicillin-sulbactam) to 100% (Table 5). For *P. aeruginosa* ($n = 8$ isolates), the EAs and CAs ranged from 50% to 100%; the EA and CA were particularly low for ceftazidime (50%) and EA was low for gentamicin (75%) (Table 5). For the two *A. baumannii* isolates, the CAs were 100% for all the drugs tested (EA was not applicable, as testing was performed by disk diffusion) (Table 5).

Workflow. Workflow results are presented in Table 7. When using the Accelerate Pheno system for positive blood cultures, the times to identification and susceptibility were reduced by 23.47 h and 41.86 h, respectively; the hands-on time per positive culture was reduced by 25.5 min.

Overviews of the workflows associated with the SOC and the AXDX for Gram-positive organisms are shown in Fig. 1 and 2.

DISCUSSION

We evaluated the performance of the Accelerate Pheno system for the identification and antimicrobial susceptibility of organisms directly from positive blood culture bottles. To our knowledge, this is the first study to evaluate the workflow and real-time

TABLE 5 Performance characteristics of the Accelerate Pheno system for Gram-negative AST performance by antibiotic and organism grouping^a

Antibiotic	EA		CA		No. of results					
	No. results/total ^b	%	No. results/total ^c	%	VME	ME	MIe	S	I	R
<i>Enterobacteriaceae</i>										
Amikacin	61/61	100	61/61	100	0	0	0	60	0	1
Ampicillin-Sulbactam	31/37	83.8	30/37	81.1	0	1 ^e	6	18	6	13
Cefazolin ^d	42/47	89.4	40/47	85.1	0	0	7	0	40	7
Cefepime	59/63	93.7	59/63	93.7	0	0	4	58	2	3
Ceftazidime	52/62	83.9	55/62	88.7	0	1	6	54	0	8
Ceftriaxone	62/62	100	60/62	96.8	0	0	2	54	0	8
Ciprofloxacin	61/62	98.4	60/62	96.8	0	0	2	45	1	16
Colistin ^d	NA ^f	NA ^g	1/1	100	0	0	0	1	0	0
Ertapenem	62/63	98.4	59/63	93.7	0	1	3	60	2	1
Gentamicin	60/63	95.2	63/63	100	0	0	0	56	1	6
Meropenem	60/60	100	60/60	100	0	0	0	59	0	1
Tobramycin	58/61	95.1	58/61	95.1	0	0	3	50	6	5
Total	608/641	94.9	606/642	94.4	0	3	33	515	58	69
<i>Pseudomonas aeruginosa</i>										
Amikacin	8/8	100	8/8	100	0	0	0	7	0	1
Cefepime	8/8	100	7/8	87.5	0	0	1	7	0	1
Ceftazidime	4/8	50	4/8	50	0	0	4	7	1	0
Ciprofloxacin	7/7	100	7/7	100	0	0	0	6	0	1
Colistin ^d	NA	NA ^g	1/1	100	0	0	0	1	0	0
Gentamicin	6/8	75	8/8	100	0	0	0	7	0	1
Meropenem	8/8	100	8/8	100	0	0	0	7	0	1
Tobramycin	7/7	100	7/7	100	0	0	0	6	0	1
Total	48/54	88.9	50/55	90.9	0	0	5	48	1	6
<i>Acinetobacter baumannii</i>										
Amikacin	NA	NA	2/2	100	0	0	0	2	0	0
Ampicillin-sulbactam ^d	NA	NA	2/2	100	0	0	0	2	0	0
Cefepime ^d	NA	NA	2/2	100	0	0	0	2	0	0
Ciprofloxacin ^d	NA	NA	2/2	100	0	0	0	2	0	0
Meropenem ^d	NA	NA	2/2	100	0	0	0	2	0	0
Piperacillin-tazobactam	NA	NA	1/1	100	0	0	0	1	0	0
Total	NA	NA	11/11	100	0	0	0	11	0	0
Overall	656/695	94.4	667/708	94.2	0	3	38	574	59	75

^aResults based on CLSI 2016 breakpoints.^bValues are the numbers of results within one doubling dilution of the reference results over the total numbers of test results.^cValues are the numbers of results with same categorical interpretation as the reference results over the total numbers of test results.^dIncludes data from one or more organism/antimicrobial combinations that are research use only (RUO) and not for use in diagnostic procedures.^eFor this ME, Accelerate had an MIC of 32 µg/ml (R), Vitek 2 had an MIC of 16 µg/ml (I), and broth microdilution had an MIC of 8 µg/ml (S), such that all results were around the breakpoints.^fNA, not applicable.^gRUO colistin tested by disk diffusion.

performance characteristics of the system for both Gram-positive and Gram-negative organisms from fresh blood cultures in a routine diagnostic setting and for a broad patient population.

The Accelerate Pheno system performed well for the identification of bloodstream pathogens, correctly identifying 95.6% of organisms. The performance was good for Gram-positive and Gram-negative organisms, with an overall sensitivity and specificity of 95.6% and 99.5%, respectively. There were 16 false-positive and 9 false-negative results, some of which were due to the presence of off-panel organisms. Moreover, this study was performed using software v1.0; updated software is now available (v1.2.1) and incorporates interpretive rules that may limit FP (specifically for *C. glabrata*, coagulase-negative staphylococci, and *S. aureus*) and FN (specifically for *Enterobacter* spp. and *P. aeruginosa*) results in addition to decreasing invalid rates.

The system also performed well for antimicrobial susceptibility, achieving an overall essential agreement of 95.1% and categorical agreement of 95.5% compared to routine methods. There was one VME, 3 MEs, and 41 MiEs.

TABLE 6 Performance characteristics of the Accelerate Pheno system for resistance phenotype test performance

Combination	Count	CA		No. of results			
		No. results/total ^a	%	VME	ME	S	R
Cefoxitin and <i>S. aureus</i>	17	17/17	100	0	0	10	7
Cefoxitin and CNS ^b	40	39/40	97.5	1	0	16	24

^aValues are the numbers of results with same categorical interpretation as the reference results over the total numbers of test results.

^bCNS, coagulase-negative *Staphylococcus* spp.

The study was limited by the organisms isolated during the study period at a single institution. For some organisms, very few isolates were tested (e.g., only 2 *A. baumannii* isolates); more would be needed for an optimal determination of system performance. Moreover, there were only 2 vancomycin-resistant enterococci (VRE) and 1 carbapenem-resistant *Enterobacteriaceae* tested. Additional resistant organisms would be useful to further challenge the system's performance, particularly for specific antimicrobials that might only be tested on resistant organisms (i.e., RUO colistin in our institution). For polymicrobial cultures, AST results were reported only for the dominant on-panel organism and were not reported for samples where 2 or more on-panel, AST-eligible organisms were identified.

Furthermore, identification was achieved at the genus level only for some organisms, such as *Streptococcus* species; it would be preferred to achieve a species-level ID for such isolates, as identification to the species level can be critical and would still have to be performed using alternative methodologies. Additionally, in some cases, the AST results are limited and reporting is not always feasible when one does not have the full species identification, as MICs and interpretations may vary depending on the species identified. This was not a significant issue for the *Enterobacteriaceae* identified only to the genus level, as the CLSI M100-27 groups these together. For example, *K. pneumoniae* has the same reporting requirements as *K. oxytoca*; therefore, identifying the isolate as a *Klebsiella* spp. would not impact AST reporting. However, there may be challenges, even within this group. For example, *P. mirabilis* and *P. vulgaris* have different intrinsic resistance profiles (CLSI M100-S27, appendix B). Although the AXDX provides AST results for *Proteus* spp., a *P. vulgaris* isolate might test as susceptible to the penicillins or cephalosporins, though it should still be reported as resistant, as per its intrinsic resistance profile (CLSI M100-S27, appendix B1). This is not true for *P. mirabilis*. In cases like this, the laboratory may have to perform additional identification and susceptibility testing.

The greater challenge lies with the Gram-positive organisms, particularly, the *Strep-*

TABLE 7 Workflow summary of SOC versus AXDX^a

Category	SOC Workflow	AXDX Workflow	Difference (SOC – AXDX)
No. of intervention points for:			
Gram-positive organisms	12	5	7
Gram-negative organisms	12	5	7
Yeast	6	4	2
Technician hands-on time for ID and AST (min)	35.5	<10	25.5
Time to result for patient specimen from positive blood culture (min [h])			
ID	1,494 (24.9)	85.5 (1.43)	1,408.5 (23.47)
AST	2,937.5 (48.95)	425.5 (7.09)	2,512 (41.86)
Technician needed	Yes	For prep only	Time savings
Process	Manual	Automated	Technician autonomy
Wait time	Exceeds 24 h and covers shift changes	Within 1 shift	Wait time is minimized

^aSOC, standard of care; AXDX, Accelerate Pheno system.

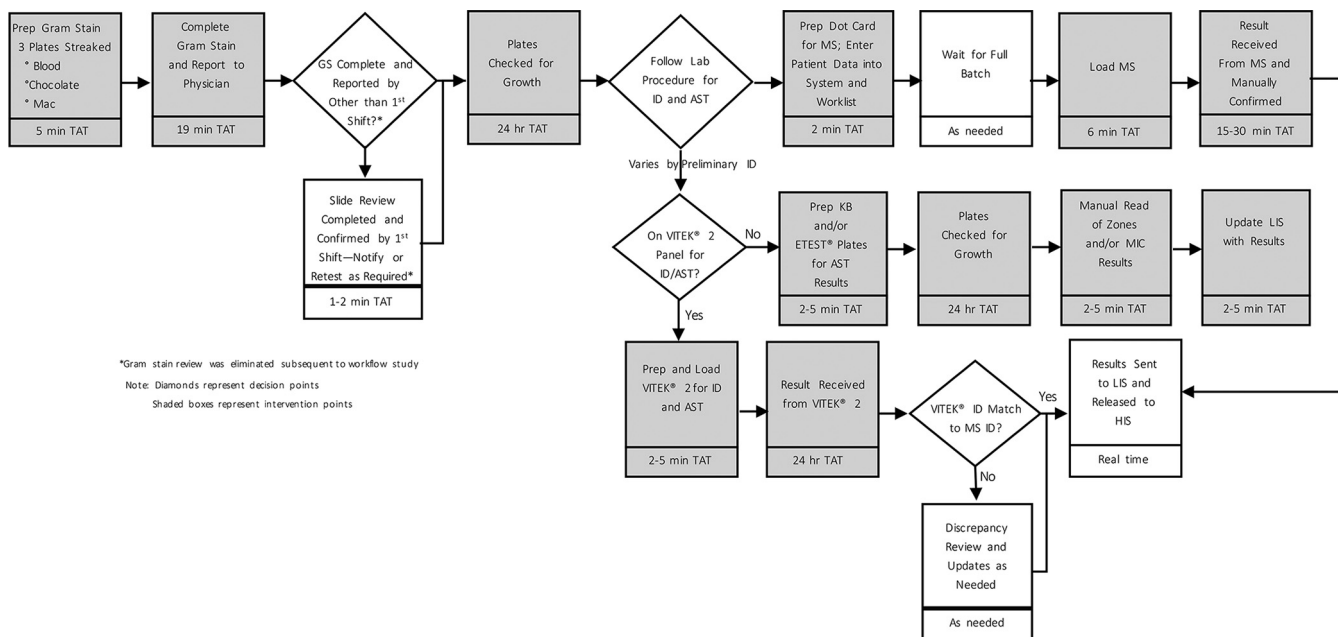


FIG 1 Overview of workflow for the standard of care for Gram-positive blood cultures.

Staphylococcus spp., for which the antimicrobials tested and interpretations reported can vary greatly depending on the species present. In the present study, a comparison of MIC results could not be performed for the *Streptococcus* species isolates, as they are identified to the genus level only by the AXDX and antimicrobial testing and reporting can only follow species identification for this group.

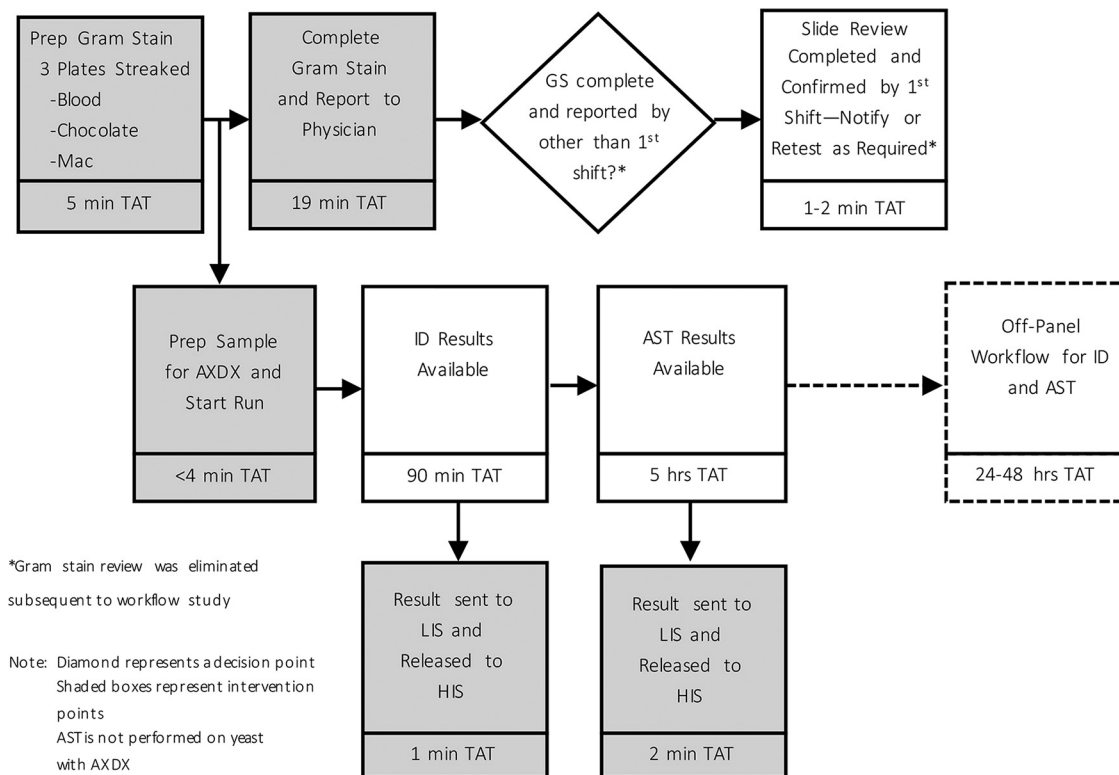


FIG 2 Overview of workflow with the Accelerate Pheno system (AXDX) for positive blood cultures.

Moreover, additional AST testing may have to be performed in a number of cases, as the antimicrobials assessed in this study were limited, particularly for the Gram-positive organisms, for which only ampicillin, erythromycin, linezolid, trimethoprim-sulfamethoxazole, vancomycin, and ceftoxitin were compared between the AXDX and the SOC. While daptomycin, ceftaroline, and doxycycline were tested using the AXDX, SOC data were not available for comparative analysis. A larger selection of antimicrobials from different classes was assessed for the Gram-negative organisms.

Furthermore, an identification to the species level may be important for epidemiologic and infection control purposes, even if not critical for reporting AST results.

Finally, certain organism-antimicrobial combinations did not perform well, such as ceftazidime for *P. aeruginosa*; further studies are needed to determine the acceptability of using this system for testing this particular combination. A limitation of the system is that it can process only one sample at a time per module, although it can currently accommodate up to 4 modules. In addition, samples have to be processed within 8 h, and the system currently does not include ID and AST for Gram-positive rods or AST for yeast.

An adoption of lean principles in the microbiology laboratory is highly desirable to provide better operational success, to standardize processes, to reduce costs, and ultimately, to provide better patient care (21, 22). The Accelerate Pheno system is a streamlined "sample-to-result" platform that has laboratory information system (LIS) connectivity. In our study, the average hands-on time per specimen was reduced by 25.5 min from routine testing, similar to the 30-min reduction described by Romano et al. (23). The time to ID based on a single specimen was observed to be 85.5 min from the time of positive blood culture (cartridge set up, 3.5 min; run on the platform, 82 min). In the United States, FDA marketing authorization requires the results to be interpreted in conjunction with Gram stain results. The time to ID is similar to that for multiplex PCR methods (13) and compared to the SOC was reduced by 23.47 h. The Accelerate Pheno system required 7.09 h to deliver susceptibility results and, compared to the 48.95 h required for the SOC results, significantly reduces the time for AST by 41.86 h. The times to ID/AST were similar to the times noted by other authors using the Accelerate Pheno system (24, 25). The integration of the Accelerate Pheno system with LIS for automated resulting, with the implementation of an automated LIS alert (either by text paging or email), will deliver actionable results to a stewardship team or provider. This test will increase the availability of results around the clock; this might require changes in practice by stewardship teams or covering physicians so that targeted antimicrobial coverage is implemented when laboratory results are ready. The capacity on the current Accelerate Pheno system is restricted to one sample per instrument module at a time. An institution might need multiple modules, depending on the volume of blood cultures with detectable growth. The system has a small footprint and several modules could be easily placed on the benchtop, allowing easy installation even in small laboratories. On the basis of our laboratory's procedures and policies for working up unique positive blood cultures, we typically see between 3 and 4 samples per day that require full identification and susceptibility testing. These would be eligible for testing with the AXDX and would require a minimum of 2 modules.

On the basis of our workflow analysis, there are 2 to 7 fewer technician intervention points in the workflow depending on which organisms are encountered in the positive blood culture (Gram-positive versus Gram-negative versus yeast) if the Accelerate Pheno system is used. The manual steps required were significantly reduced with the system, allowing time savings, greater technologist autonomy, and decreased wait times.

As with many new laboratory instruments, any return-on-investment calculations should take factors outside the laboratory into account to the extent possible; these factors include the antimicrobial costs, the length of stay, and the impacts on patient care and outcomes.

If susceptibility result reporting is coupled with antimicrobial stewardship intervention, the impact on patient care can be greater than that reported in earlier studies,

which used limited AST results based on genotypic determinants (3, 4, 9, 14, 15) rather than a fuller panel of phenotypic organism-antimicrobial susceptibility results that are available 41.86 h sooner. Additional studies are needed to show the impacts on costs, reducing the risk of adverse drug effects, reducing the pressure for resistance development, optimizing and de-escalating therapies, possibly reducing LOS, and improving patient outcomes.

In conclusion, the Accelerate Pheno system provides fast and accurate results for most of the organisms found routinely in blood cultures. A failure to identify species was due in most cases to invalids or the presence of an off-panel organism not found on the Accelerate PhenoTest BC kit panel. The Accelerate Pheno system is easy to use, reduces hands-on time for ID/AST of common blood pathogens, and allows clinically actionable results to be released much earlier than the current standard of care. For antimicrobial susceptibility, the Accelerate Pheno system performed comparably to our current AST methodologies for the majority of organism-antimicrobial combinations. However, additional testing is needed for some organisms (i.e., *Acinetobacter baumannii* and carbapenemase-producing Gram-negative organisms), as well as for some of the organism-antimicrobial combinations that were either not well represented or that did not perform as expected.

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