ePlex® Blood Culture Identification Panels

Supporting Literature

GenMark Dx®

ePlex®

Background

Traditional microbiology methods can take days to identify the cause of a blood stream infections (BSI), increasing mortality up to 8% for every hour effective antibiotics are delayed.[1] Rapid organism identification in combination with Antimicrobial Stewardship has been shown to decrease time to targeted therapy for BSI by roughly 24 hours, while decreasing hospital length of stay by 2.5 days.[2,3]

Rapid Identification

The ePlex® BCID Panels are automated, qualitative multiplex nucleic acid *in vitro* diagnostic tests, combining electrowetting and GenMark's eSensor® technology, for the simultaneous detection and identification of gram-positive (GP), gram-negative (GN) and fungal pathogens as well as antibiotic resistance genes within approximately 1.5 hours from positive blood culture following gram staining. This allows treatment decisions to occur days earlier than with conventional methods.

Broadest Coverage

The ePlex BCID Panels have the broadest molecular coverage of organisms and resistance markers based on the prevalence of pathogens that can lead to sepsis, including anaerobes and multidrug resistant organisms (MDRO), as well as common and emerging fungal pathogens.

Streamline Interpretation

The ePlex System integrates the diagnostic workflow from order-to-report and helps fast-track treatment intervention with unique capabilities designed to automate the interpretation of local antibiograms.

GenMark Dx®

1. Kumar, et al. (2006) Crit Care Med. 34 (6): 1589-1596
2. Box, et. al., (2015) Pharmacotherapy, 35 (3): 269-276.
3. Timbrook, et al. (2017) Clin Infect Dis. 64 (1): 15-23.

GenMarkDx.com

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Sepsis: A Race Against Time

Maurin, M.
Article: Practical Patient Care

The timely, accurate diagnosis of bloodstream infections poses a significant challenge to hospitals, patients and their families. These life-threatening complications also represent a high medical and economic burden for society. **GenMark Diagnostics** is looking to transform the diagnosis of sepsis with the ePlex blood culture identification solution. Professor Max Maurin from CHU Grenoble Alpes shares his perspective on sepsis and GenMark's solution.

Could you explain the clinical impact of sepsis?

Professor Max Maurin: Sepsis is an extremely critical medical condition, affecting nearly 30 million people worldwide every year. Managing sepsis is challenging given that, for every hour of treatment delay, the mortality rate increases by around 8%.

The situation has recently worsened due to the emergence of multidrug resistant (MDR) pathogens, increasing the risk of administration of non-adapted empirical antibiotic therapy. Due to their severity, bloodstream infections (BSIs) are the most expensive condition treated in most hospitals.

What are the unmet clinical needs involved in managing sepsis?

While traditional bacteriological methods are effective at identifying the causative organisms and their antibiotic susceptibilities, it usually takes at least two days to get these results. During this time, patients will receive empirical antibiotic therapy that may be poorly effective against MDR pathogens, increasing the risk of severe complications and death. Moreover, this broad-spectrum therapy favours selection of new resistances in the commensal microflora.

There is an urgent need to develop innovative technologies that enable faster identification of an involved pathogen, as well as detection of resistances to first-line drugs, in order to allow rapid optimisation of therapy. The ideal situation would be to detect microorganisms directly in the patient's blood samples but, at present, this goal remains unattainable. The current best alternative is to rapidly determine the pathogen and its resistance markers from blood bottles flagged positive after incubation. This would allow the clinician to adapt the antibiotics at least 24 hours earlier than current practice, with an expected significant improvement in patient outcome.

Could you describe the ePlex BCID solution?

GenMark took a unique approach in offering three individual panels for detection of gram-positive bacteria, gram-negative bacteria and fungi. The panels allow rapid detection of microorganisms most frequently involved in BSIs and critical antibiotic resistance markers for bacteria. The appropriate panel is selected based on the gram-stain result of the blood culture, which remains a critical step in BCID analysis.

Thanks to the innovative, multiplex approach being developed by GenMark, the organism identification and resistance markers can be obtained within approximately an hour and a half from the positive blood culture, which is a technological breakthrough that allows significant improvement in the management of patients.

How will the ePlex BCID solution help address the threat of antibiotic resistance?

In our laboratory, we perform antibiotic susceptibility testing (AST) following MALDI-TOF MS identification of the isolated pathogen to guide antibiotic therapy, which takes around two days. Patients with a BSI generally stay on empiric therapy until those results are available. With ePlex BCID, we expect to review identification and resistance marker results within about an hour and a half from the blood culture flagging positive, allowing treatment decisions much sooner than before.

For complex antibiotic-resistance mechanisms, the GenMark approach may allow accurate identification of the involved resistance gene, while AST may only provide various hypothetical mechanisms, which will have to be confirmed by additional tests. The GenMark system, therefore, helps to ensure that some of the most common resistance mechanisms won't be missed and resistant infections won't be left untreated or transmitted to other patients, which is critical to improving infection control and antibiotic stewardship efforts. The goal is always to get more actionable information earlier to drive improvements in patient care and outcomes.

> "The GenMark approach may allow accurate identification of the involved resistance gene, while AST may only provide various hypothetical mechanisms."

How do you see ePlex BCID improving patient care?

Sepsis is life-threatening, and reducing time to optimal therapy is critical. By reducing time to a more actionable answer, clinicians can enhance antibiotic stewardship, improve hospital-bed management and reduce patient length of stay. All of these factors should lead to better patient outcomes and cost savings.

Preliminary Blood Culture Rapid Identification and Resistance Target Determination using GenMark Dx ePlex® Blood Culture Identification System Improves Sepsis Management, Aids Early Antimicrobial Stewardship (AMS) Interventions and Results in Significant Cost Savings

O'Donnell, C., Griffin A., Power, A., Boyle, B.
Healthcare Infection Society, 2018

Introduction

Time to appropriate antimicrobial therapy is essential to reduce mortality and morbidity in sepsis-related bloodstream infections (BSI).[1] Standard practice for identification (ID) and antimicrobial susceptibility testing (AST) of a positive blood culture can take up to 48 hours.[2]

GenMark Dx® ePlex® Blood Culture Identification (BCID) panels are an automated, qualitative nucleic acid multiplex in vitro diagnostic test, combining electrowetting and GenMark's eSensor® technology, for the simultaneous detection and ID of multiple gram positive (GP) and gram negative (GN) bacteria and fungi from positive blood cultures following gram staining.

- Electrowetting uses electrical fields to directly manipulate droplets on the surface of a hydrophobically coated printed circuit board.
- eSensor® technology uses a solid-phase electrochemical method for determining the presence of one or more of a defined panel of bacterial or fungal target sequences.

Molecular assays, such as the ePlex BCID panels, enable clinicians to rapidly identify clinically relevant BSI and their resistance genes when blood cultures are initially positive. This allows for early antimicrobial interventions, while quickly ruling out blood culture contamination, resulting in cost savings.

Aim

To evaluate the rapid laboratory, clinical, antimicrobial stewardship and health economic benefits of the implementation of the GenMark Dx® ePlex BCID panels.

Results

In gram stain-positive blood cultures, GenMark Dx ePlex BCID panels provide significantly superior rapid diagnostic performance, in both organism identification and resistance gene detection, compared to the Bruker's MALDI Biotyper/Sepsityper direct identification system.

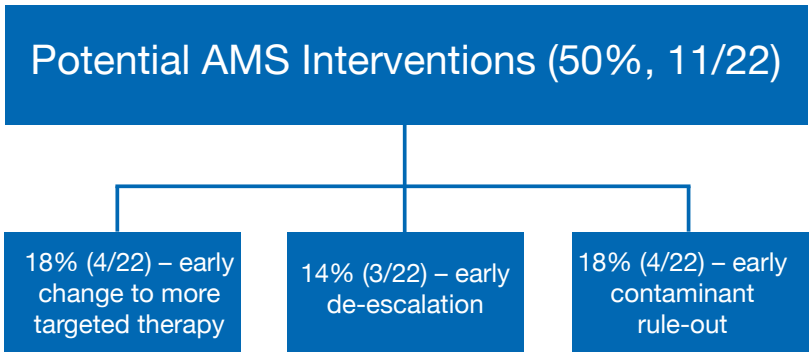
- 21 blood cultures were tested
- 2 blood cultures were mixed:
  - *Enterococcus faecium and Citrobacter* (required a GN and a GP card for ID)
  - *Staphylococcus epidermidis and Enterococcus faecalis* (required 1 GP card for ID)

Table 1 – Average Time to Identification and Resistance Profiles for GN/GP Bacteria

	ePlex System	Standard Methodology	Average Differential Time
Average Time to Identification (n=21 panels)	297 min * (4 hr 47 min)	1874 min (31 hr 14 min)	1577 min (26 hr 17 min)
Average Time to Resistance Determinants (n=15 panels)	293 min (4 hr 53 min)	3755 min (62 hr 35 min)	3462 min (57 hr 42 min)

*ePlex processing time = 90 mins. ePlex BCID panels were only used during working hours so there was a delay in some cases between blood culture flagging positive and being loaded onto the ePlex machine (i.e. if flagged positive overnight).

- The fungal ePlex ID was *Malassezia furfur**.
  - This failed to grow in our laboratory.
  - ID and AST was performed at the UK Mycology Reference Laboratory – the final report was received 38 days after the blood culture initially flagged positive.
  - Early ID allowed for an early change to an appropriate antifungal agent.
- Taking into account the selection of organisms and resistance determinants on the ePlex panel, concordance with final culture ID and AST results was 100%.
- Three isolates had no targets determined on the ePlex BCID panels and were not detected – *Prevotella denticola, Pseudomonas fluorescens/Pseudomonas pickettii and Raoultella spp.*



Although the sample set was small, the results of the ePlex BCID panels:

- Could have resulted in potentially 50% earlier AMS interventions (may increase with the sample size).
- Provided early ID of *Serratia marcescens*, *Enterobacter cloacae* complex and *Citrobacter* would have allowed more targeted therapy and improved sepsis management.
- Early ID of Staphylococcus aureus without detection of *mecA* or *mecC* resistant determinants to allow early de-escalation to targeted therapy.
- Early ID of *Enterococcus faecalis* without detection of *vanA* or *vanB* resistant determinants would allow for early de-escalation from empiric linezolid to targeted amoxicillin.
- Early ID of blood culture contaminants in the four cases could have resulted in potential savings of over €16,000 (based on local financial costings).

*The *Malassezia fufur* target is no longer included on the current BCID-FP CE IVD panel

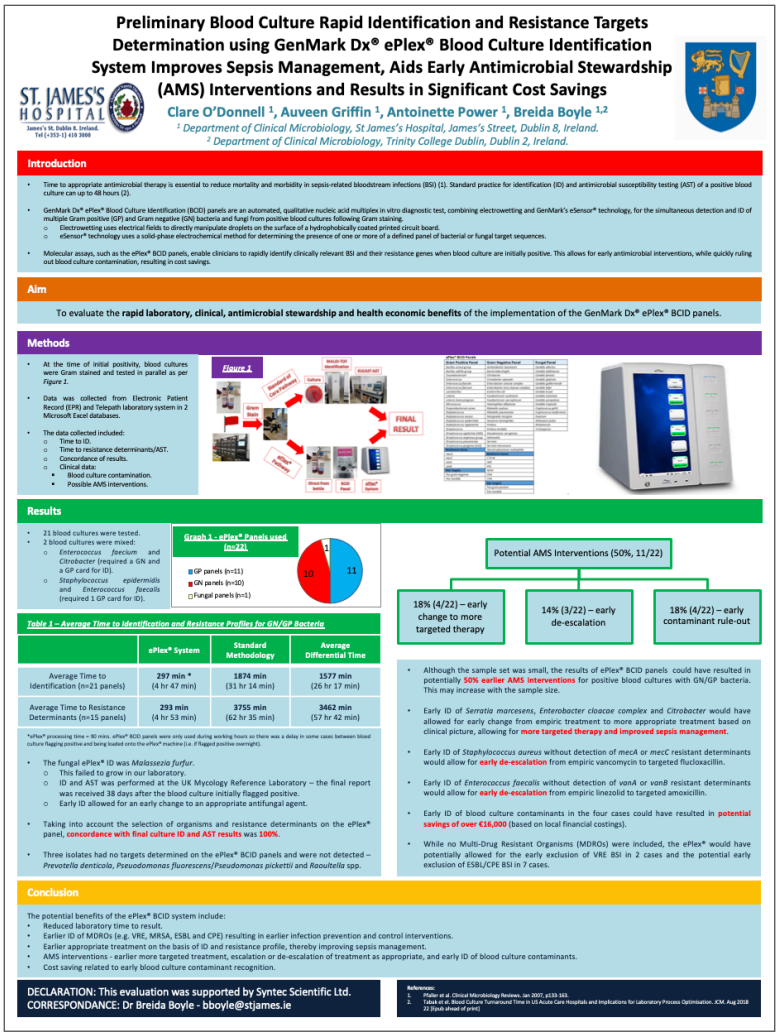
While no Multi-Drug Resistant Organisms (MDROs) were included, the ePlex would have potentially allowed for the early exclusion of VRE BSI in 2 cases and the potential early exclusion of ESBL/CPE BSI in 7 cases.

Conclusion

To evaluate the rapid laboratory, clinical, antimicrobial stewardship and health economic benefits of the implementation of the GenMark Dx® ePlex BCID panels.

The potential benefits of the ePlex BCID system include:

- Reduced laboratory time to result.
- Earlier ID of MDROs (e.g. VRE, MRSA, ESBL and CPE) resulting in earlier infection prevention and control interventions.
- Earlier appropriate treatment on the basis of ID and resistance profile, thereby improving sepsis management.
- AMS interventions - earlier more targeted treatment, escalation or de-escalation of treatment as appropriate, and early ID of blood culture contaminants.
- Cost saving related to early blood culture contaminant recognition.



Preliminary Blood Culture Rapid Identification and Resistance Targets Determination using GenMark Dx® ePlex® Blood Culture Identification System Improves Sepsis Management, Aids Early Antimicrobial Stewardship (AMS) Interventions and Results in Significant Cost Savings

ST. JAMES'S HOSPITAL

Clare O'Donnell [1], Auveen Griffin [1], Antoinette Power [1], Breida Boyle [1,2]

[1] Department of Clinical Microbiology, St James's Hospital, James's Street, Dublin 8, Ireland.
[2] Department of Clinical Microbiology, Trinity College Dublin, Dublin 2, Ireland.

Introduction

- Time to appropriate antimicrobial therapy is essential to reduce mortality and morbidity in sepsis-related bloodstream infections (BSI) (1). Standard practice for identification (ID) and antimicrobial susceptibility testing (AST) of a positive blood culture can up to 48 hours (2).
- GenMark Dx® ePlex® Blood Culture Identification (BCID) panels are an automated, qualitative nucleic acid multiplex in vitro diagnostic test, combining electrowetting and GenMark's eSensor® technology, for the simultaneous detection and ID of multiple Gram positive (GP) and Gram negative (GN) bacteria and fungi from positive blood cultures following Gram staining.
  - Electrowetting uses electrical fields to directly manipulate droplets on the surface of a hydrophobically coated printed circuit board.
  - eSensor® technology uses a solid-phase electrochemical method for determining the presence of one or more of a defined panel of bacterial or fungal target sequences.
- Molecular assays, such as the ePlex® BCID panels, enable clinicians to rapidly identify clinically relevant BSI and their resistance genes when blood culture are initially positive. This allows for early antimicrobial interventions, while quickly ruling out blood culture contamination, resulting in cost savings.

Aim

To evaluate the **rapid laboratory, clinical, antimicrobial stewardship and health economic benefits** of the implementation of the GenMark Dx® ePlex® BCID panels.

Methods

- At the time of initial positivity, blood cultures were Gram stained and tested in parallel as per *Figure 1*.
- Data was collected from Electronic Patient Record (EPR) and Telepath laboratory system in 2 Microsoft Excel databases.
- The data collected included:
  - Time to ID.
  - Time to resistance determinants/AST.
  - Concordance of results.
  - Clinical data:
    - Blood culture contamination.
    - Possible AMS interventions.

Figure 1.

Results

- 21 blood cultures were tested.
- 2 blood cultures were mixed:
  - *Enterococcus faecium* and *Citrobacter* (required a GN and a GP card for ID).
  - *Staphylococcus epidermidis* and *Enterococcus faecalis* (required 1 GP card for ID).

Graph 1 - ePlex® Panels used (n=21)

Table 1 – Average Time to Identification and Resistance Profiles for GN/GP Bacteria

	ePlex® System	Standard Methodology	Average Differential Time
Average Time to Identification (n=21 panels)	**297 min** * (4 hr 47 min)	**1874 min** (31 hr 14 min)	**1577 min** (26 hr 17 min)
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- The fungal ePlex® ID was *Malassezia furfur*.
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  - Early ID allowed for an early change to an appropriate antifungal agent.
- Taking into account the selection of organisms and resistance determinants on the ePlex® panel, **concordance with final culture ID and AST results was 100%.**
- Three isolates had no targets determined on the ePlex® BCID panels and were not detected – *Prevotella denticola*, *Pseudomonas fluorescens/Pseudomonas pickettii* and *Raoultella* spp.

Potential AMS Interventions (50%, 11/22)

- 18% (4/22) – early change to more targeted therapy
- 14% (3/22) – early de-escalation
- 18% (4/22) – early contaminant rule-out

- Although the sample set was small, the results of ePlex® BCID panels could have resulted in potentially **50% earlier AMS interventions** for positive blood cultures with GN/GP bacteria. This may increase with the sample size.
- Early ID of *Serratia marcesens*, *Enterobacter cloacae complex* and *Citrobacter* would have allowed for early change from empiric treatment to more appropriate treatment based on clinical picture, allowing for **more targeted therapy and improved sepsis management.**
- Early ID of *Staphylococcus aureus* without detection of *mecA* or *mecC* resistant determinants would allow for **early de-escalation** from empiric vancomycin to targeted flucloxacillin.
- Early ID of *Enterococcus faecalis* without detection of *vanA* or *vanB* resistant determinants would allow for **early de-escalation** from empiric linezolid to targeted amoxicillin.
- Early ID of blood culture contaminants in the four cases could have resulted in **potential savings of over €16,000** (based on local financial costings).
- While no Multi-Drug Resistant Organisms (MDROs) were included, the ePlex® would have potentially allowed for the early exclusion of VRE BSI in 2 cases and the potential early exclusion of ESBL/CPE BSI in 7 cases.

Conclusion

The potential benefits of the ePlex® BCID system include:
- Reduced laboratory time to result.
- Earlier ID of MDROs (e.g. VRE, MRSA, ESBL and CPE) resulting in earlier infection prevention and control interventions.
- Earlier appropriate treatment on the basis of ID and resistance profile, thereby improving sepsis management.
- AMS interventions - earlier more targeted treatment, escalation or de-escalation of treatment as appropriate, and early ID of blood culture contaminants.
- Cost saving related to early blood culture contaminant recognition.

DECLARATION: This evaluation was supported by Syntec Scientific Ltd.
CORRESPONDANCE: Dr Breida Boyle - bboyle@stjames.ie

References:
1. Pfaller et al. Clinical Microbiology Reviews. Jan 2007, p133-163.
2. Tabak et al. Blood Culture Turnaround Time in US Acute Care Hospitals and Implications for Laboratory Process Optimisation. JCM. Aug 2018 22 [Epub ahead of print]

1. Pfaller et al. Clinical Microbiology Reviews. Jan 2007, p133-163.

2. Tabak et al. Blood Culture Turnaround Time in US Acute Care Hospitals and Implications for Laboratory Process Optimisation. JCM. Aug 2018 22 [Epub ahead of print]

The War on Drug Resistance

The global antimicrobial-resistance epidemic is of concern to all healthcare workers, especially when it comes to sepsis. **GenMark**, a leading provider of diagnostic solutions designed to improve patient care, is launching a new campaign to improve the way diagnostics are implemented, especially when it comes to microbial detection. Max Maurin, professor of clinical microbiology at Grenoble University Hospital, and Tristan Timbrook, an antimicrobial stewardship pharmacist, speak to Practical Patient Care about the path forward.

The importance of stewardship programmes in patient care settings is something that many are trying to promote, especially when it comes to highlighting the value of rapid pathogen and antibiotic resistance gene detection (ARGD) in improving sepsis outcomes. More and more people are dying of microbial resistance, and new strategies are needed for rapid identification to enhance patient care and improve antimicrobial stewardship.

The importance of rapid detection

"The emergence of multidrug resistance (MDR) in common human pathogens has dramatically increased the risk of treatment failure related to the administration of inappropriate empirical therapy," says Max Maurin, professor of clinical microbiology at Grenoble University Hospital. "In order to reduce this risk, the antimicrobial spectrum of empirical treatment has been gradually expanded, but this has contributed to the rapid emergence of new resistances."

Tristan Timbrook, an antimicrobial stewardship pharmacist, agrees with his peer.

"For every hour that a sepsis patient goes without effective antimicrobial therapy, mortality increases by 8%," he explains.

"Conventional microbiology techniques typically require days to provide actionable results. Therefore, in patients with sepsis and bacteraemia or septicaemia, the rapid identification of pathogens and antibiotic resistance genes can have profound value and impact on patient clinical outcomes by ensuring timely prescribing of effective antimicrobial therapy." Time to effective and optimal therapy can "translate into improved clinical outcomes including decreased mortality, length of stay, avoidance of adverse drug effects and healthcare financial expenditures."

The benefits of rapid resistance gene detection have been noted. Acquired resistances to antimicrobials are usually determined by phenotypic methods – such as the antibiogram – which currently provide final results two days or more after clinical sample collection for isolation of the pathogen, says Maurin. But rapid molecular diagnostic technologies can improve patient outcomes in septicaemia through detection of resistance genes and organisms, and the use of resistance detection may help to decrease unnecessary broad-spectrum antibiotics, decreasing resistance and infections."

The importance of rapid detection

In comparing ARGD to antibiotic susceptibility testing (AST) alone, ARGD adds value to AST because it allows more rapid determination of effective therapy than any currently FDA-approved phenotypic techniques. Resistance gene detection can complement AST in ways not readily apparent, and can reflect resistance genes that may not be phenotypically identified by AST.

What more can be done by hospital infection control and prevention (ICP) with routine antibiotic resistance gene results?

"With routine antibiotic resistance gene results, hospital ICP can improve the ability to isolate patients," says Timbrook. "These also allow for the faster removal of contact precautions in patients without the need as contact precautions, while important and helpful, have been shown to be burdensome to patient care."

Maurin agrees: "rapid detection of microorganisms with multidrug or high-level resistances to antibiotics in infected patients and/or carriers is of tremendous importance to limit their spread in hospital settings."

The future of bloodstream infection diagnostics will likely not be solely phenotypic or genotypic methods, according to Timbrook, but more likely a "combination thereof, similar to HIV testing, as they provide complementary information."

Technologies in practice

It is worth noting that studies have demonstrated antimicrobial stewardship programmes are essential in achieving these outcomes by facilitating appropriate and timely use of rapid diagnostic results. Unfortunately, survey data has suggested that – at most – only 30% of hospitals use these potentially life-saving diagnostic technologies in patients with septicaemia.

Increasing antimicrobial resistance is currently a global public health threat and the continued problem of resistance is unavoidable. However, with antibiotic use being a principal driver of increasing antibiotic resistance, rapid diagnostics facilitated by antimicrobial stewardship programmes can improve the use of targeted narrow spectrum antibiotics to avoid unnecessary selection for antibiotic resistance. Adoption of these new rapid technologies, used in conjunction with antimicrobial stewardship programmes and clinician education for awareness on antimicrobial resistance issues, will no doubt help to turn the tide in antimicrobial resistance.

Ultimately, the barriers to improving sepsis patient outcomes are numerous, and a return to a more favourable situation will require sustained efforts to eliminate such MDR populations, especially in hospital settings.

ePlex®

Benefits of Rapid Diagnostic Tests

The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis

Timbrook, T., Morton J., McConeghy, K., Caffrey, A., Mylonakis, E. and LaPlante, K.L.
Clinical Infectious Diseases - 2017

Abstract

Background
Previous reports on molecular rapid diagnostic testing (mRDT) do not consistently demonstrate improved clinical outcomes in bloodstream infections (BSIs). This meta-analysis seeks to evaluate the impact of mRDT in improving clinical outcomes in BSIs.

Methods
We searched PubMed, CINAHL, Web of Science, and EMBASE through May 2016 for BSI studies comparing clinical outcomes between mRDT and conventional microbiology methods.

Results
Thirty-one studies were included with 5920 patients. The mortality risk was significantly lower with mRDT than with conventional microbiology methods (odds ratio [OR], 0.66; 95% confidence interval [CI], .54-.80), yielding a number needed to treat of 20. The mortality risk was slightly lower with mRDT in studies with antimicrobial stewardship programs (ASPs) (OR, 0.64; 95% CI, .51-.79), and non-ASP studies failed to demonstrate a significant decrease in mortality risk (0.72; .46-1.12). Significant decreases in mortality risk were observed with both gram-positive (OR, 0.73; 95% CI, .55-.97) and gram-negative organisms (0.51; .33-.78) but not yeast (0.90; .49-1.67). Time to effective therapy decreased by a weighted mean difference of -5.03 hours (95% CI, -8.60 to -1.45 hours), and length of stay decreased by -2.48 days (-3.90 to -1.06 days).

Conclusions
For BSIs, mRDT was associated with significant decreases in mortality risk in the presence of a ASP, but not in its absence. mRDT also decreased the time to effective therapy and the length of stay. mRDT should be considered as part of the standard of care in patients with BSIs.

Panels for Fast Sepsis Diagnosis

When sepsis strikes, every hour counts. But traditional antimicrobial susceptibility testing can take up to 72 hours and doesn't always identify the genes that make bacteria resistant to treatment. Clinical microbiologist Dr. Cathal Collins from Ireland's Cavan General Hospital discusses how new testing panels from **GenMark** are changing the game for sepsis diagnosis.

Why is it important to diagnose the cause of sepsis early?

Dr Cathal Collins: We are always endeavouring with regard to sepsis to shorten the time between the clinical diagnosis and the diagnosis of the cause, as we know this can impact on patient outcome. Knowledge of the causative organism aids antimicrobial decision-making, provides support for a clinically-made diagnosis or provides a clue regarding the sepsis source if it is not clinically apparent. If organism identification has infection control or public health consequences, the earlier appropriate control measures are instigated, the more successful these measures are likely to be.

What are the advantages of identifying antibiotic resistance genes over normal methods of antimicrobial susceptibility testing?

The methods employed to detect antibiotic resistance genes tend to provide information much more rapidly than phenotypic ones. Early knowledge of certain resistance genes can identify agents that should probably be avoided in treating the patient. Detecting the presence of resistance mechanisms can also sometimes be difficult with phenotypic methods alone. Finally, identification of antibiotic resistance genes gives infection control practitioners more detailed information than what phenotypic methods can do.

What effects does this have on patient care?

Whenever possible, the organism identity and its susceptibility profile should be determined as soon as possible, so that targeted antimicrobial therapy can be provided. Antimicrobial resistance is a major concern these days and our chances of being wrong with empiric antimicrobial prescribing decisions are increasing all the time in pretty much all parts of the world. We know that the sooner appropriate antimicrobial therapy is administered in sepsis, particularly in the critically ill, the better the outcome for the patient.

What has your experience been of using GenMark's ePlex blood culture identification panels to identify resistance genes?

I can say that ePlex has significantly changed the way we deal with blood cultures. The medical laboratory scientists are happy with its ease of use and hands-on time per test, and we can provide clinicians more detailed information much sooner – within a couple of hours of a positive blood culture, rather than days. I love that I no longer have to wait on overnight cultures to determine if that gram-positive coccus that looks like a *Staphylococcus* spp on the gram stain is an MSSA/MRSA or not. This sort of information allows targeted therapy and helps to avoid the unnecessary addition of antimicrobials. In fact, the performance of the ePlex is such that we are now considering not routinely performing any subcultures from peripheral blood cultures where staphylococci are suspected on the gram stain, and the ePlex has indicated that neither *S. aureus or S. lugdunensis* are present.

Can you tell us about a case study?

We had a patient recently who was diagnosed with a hepatic abscess and had a blood-culture flagging positive with gram-negative bacilli and gram-positive diplococci within six hours of collection. Within a couple of hours of the gram result, the ePlex panel had detected the presence of *Escherichia coli* with an extended-spectrum beta-lactamase (ESBL) resistance gene (CTX-M) and an *Enterococcus faecium* with a vancomycin resistance gene (vanA). The patient's antibacterial regimen was changed from piperacillin-tazobactam and gentamicin to linezolid and meropenem shortly after. Standardised culture-based susceptibility results only became available two days later and confirmed the presence of an ESBL-producing piperacillin-tazobactam-resistant *E. coli* and a vancomycin-resistant *Enterococcus faecium*.

What effects have you seen on patient outcomes in general at Cavan General Hospital since these panels came into play?

We're a small hospital with about 220 acute-care beds and have only been using these panels routinely for our blood cultures since January, so we don't have any overall objective information on this yet. Anecdotally, though, we have had several cases where organism identification and/or the detection of resistance markers in blood from the gram-stain positive blood culture has resulted in the administration of targeted antimicrobial therapy around 24 hours sooner than would have been the case when relying solely on culture-based methodologies. This can only be good for patient outcomes.

Evaluation of the ePlex Blood Culture Identification Panels for Detection of Pathogens in Bloodstream Infections

Huang, T.D., Melnik, E., Bogaerts, P., Evrard, S., Glupczynski, Y
Journal of Clinical Microbiology - 2018

Abstract

Background
Rapid identification and susceptibility testing results are of importance for the early appropriate therapy of bloodstream infections. The ePlex (GenMark Diagnostics) Blood Culture Identification (BCID) Panels are fully automated PCR-based assays designed to identify gram-positive and gram-negative bacteria, fungi, and bacterial resistance genes within 1.5 h from positive blood culture.

Methods
Consecutive nonduplicate positive blood culture episodes were tested by the ePlex system prospectively. The choice of panel(s) (gram-positive, gram-negative, and/or fungal pathogens) was defined by gram-stained microscopy of blood culture-positive bottles (BacT/Alert; bioMérieux).

Results
Results with the ePlex panels were compared to the identification results obtained by standard culture-based workflow. In total, 216 positive blood culture episodes were evaluable, yielding 263 identification results. The sensitivity/positive predictive value for detection by the ePlex panels of targeted cultured isolates were 97% and 99% for the gram-positive panel and 99% and 96% for the gram-negative panel, resulting in overall agreement rates of 96% and 94% for the gram-positive and gram-negative panel, respectively. All 26 samples with targeted resistance results were correctly detected by the ePlex panels.

Conclusions
The ePlex panels provided highly accurate results and proved to be an excellent diagnostic tool for the rapid identification of pathogens causing bloodstream infections. The short time to results may be of added value for optimizing the clinical management of patients with sepsis.

Superior Rapid Diagnostic Performance in Gram Stain-Positive Blood Cultures with the GenMark Dx ePlex Blood Culture Identification Panels Compared to Bruker's MALDI Biotyper/Sepsityper System

Gilmartin, F., Sheehan, R., Crowe, L., O'Neill, L., Collins, C.J.
European Congress of Clinical Microbiology & Infectious Diseases - 2018

Introduction

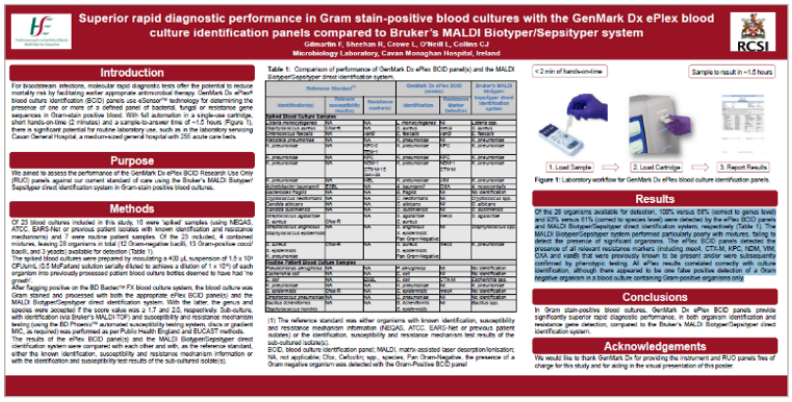
For bloodstream infections, molecular rapid diagnostic tests offer the potential to reduce mortality risk by facilitating earlier appropriate antimicrobial therapy. GenMark Dx ePlex® blood culture identification (BCID) panels use eSensorTM technology for determining the presence of one or more of a defined panel of bacterial, fungal or resistance gene sequences in gram-stain positive blood. With full automation in a single-use cartridge, short hands-on-time (2 minutes) and a sample-to-answer time of ~1.5 hours, there is significant potential for routine laboratory use, such as in the laboratory servicing Cavan General Hospital, a medium-sized general hospital with 255 acute care beds.

Results

Of the 28 organisms available for detection, 100% versus 68% (correct to genus level) and 93% versus 61% (correct to species level) were detected by the ePlex BCID panels and MALDI Biotyper/Sepsityper direct identification system, respectively (Table 1). The MALDI Biotyper/ Sepsityper system performed particularly poorly with mixtures, failing to detect the presence of significant organisms. The ePlex BCID panels detected the presence of all relevant resistance markers (including mecA, CTX-M, KPC, NDM, VIM, OXA and vanB) that were previously known to be present and/or were subsequently confirmed by phenotypic testing. All ePlex results correlated correctly with culture identification, although there appeared to be one false positive detection of a gram-negative organism in a blood culture containing gram-positive organisms only.

Conclusions

In gram stain-positive blood cultures, GenMark Dx ePlex BCID panels provide significantly superior rapid diagnostic performance, in both organism identification and resistance gene detection, compared to the Bruker's MALDI Biotyper/Sepsityper direct identification system.


Superior rapid diagnostic performance in Gram stain-positive blood cultures with the GenMark Dx ePlex blood culture identification panels compared to Bruker's MALDI Biotyper/Sepsityper system

Gilmartin F, Sheehan R, Crowe L, O'Neill L, Collins CJ
Microbiology Laboratory, Cavan Monaghan Hospital, Ireland

Introduction

Purpose

Methods

Results

Conclusions

Acknowledgements

Performance of the GenMark ePlex Blood Culture Identification Fungal Pathogen Panel: A Prospective French Bicentric Evaluation Using Clinical Samples

Maubon, D., Ait-Ammar, N., Dard, C., Angebault, C., Fauchet, N., Garnaud, C., Cornet, M., Botterel, F.
European Congress of Clinical Microbiology & Infectious Diseases - 2018

Introduction

Fungemia presents high morbidity, mortality and rapid microbiological identification contributes to adapt quickly antifungal therapy. Among kits based on molecular technologies, the ePlex blood culture identification fungal pathogen panel (ePlex BCID-FP, GenMark Dx) is a fully automated, easy-to-use cartridge designed to detect 16 fungal targets including common and emerging ones from positive blood culture (BC). This study aimed to prospectively evaluate the performance of this recently CE-IVD marked test using clinical BC samples.

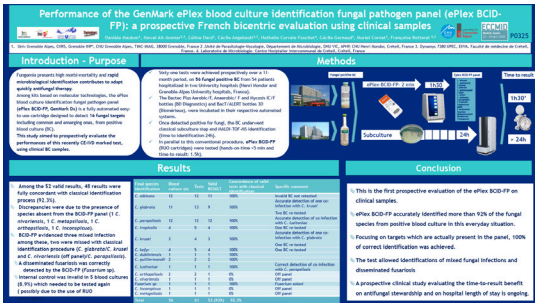
Results

- Among the 52 results, 48 were fully concordant with classical process (92.3%).
- Discrepancies were due to the presence of species absent from the BCID-FP panel including 1 *C. nivariensis*, 1 *C. metapsilosis,* 1 *C. orthopsilosis* 1 *C. inconspicua*.
- BCID-FP evidenced three mixed infections among these, two were missed with classical identification procedures (*C. glabrata*/*C. krusei* and *C. nivariensis* (off panel)/*C. parapsilosis*).
- A disseminated fusariosis was corrected detected by the BCID-FP Panel (*Fusarium* sp.).
- Internal control was invalid in 5 blood cultures (8.9%) which needed to be tested again (possibly due to the use of RUO cartridges).

Final Species Identification	Blood Culture (n)	Concordance of valid tests with classical identification	Specific Comment
C. albicans	12	100%	Invalid BC not retested
C. glabrata	11	100%	Accurate detection of one co-infection with C. *krusei*. Two BC re-tested.
C. parapsilosis	12	100%	Accurate detection of co-infection with C. *lusitaniae*
C. tropicalis	4	100%	One BC re-tested
C. krusei	3	100%	Accurate detection of one co-infection with C. *glabrata*. One BC re-tested.
C. kefyr	4	100%	One BC re-tested
C. dubliniensis	1	100%	
C. guilliermondii	2	100%	
C. lusitaniae	1	100%	Correct detection of co-infection with *C. parapsilosis*
C. orthopsilosis	2	0%	Off panel
C. nivariensis	1	0%	Off panel
Fusarium sp.	1	100%	*Fusarium solani*
C. inconspicua	1	0%	Off panel
C. metapsilosis	1	0%	Off panel
Total	**56**	**92.3%**	

Conclusions

- This the first prospective evaluation of the ePlex BCID-FP on clinical samples
- ePlex BCID-FP accurately identified more than 92% of the fungal species from positive blood culture in this everyday situation. Focusing on targets which are present in the panel, 100% of correct identification was achieved. The test allowed identifications of mixed fungal infections and disseminated *fusariosis*.
- A prospective clinical study evaluating the time-to-result benefit of antifungal stewardship and on hospital length of stay is ongoing.



ePlex® | Implementation

Implementation and Optimization of Molecular Rapid Diagnostic Tests for Bloodstream Infections

Wenzler, E., Timbrook, T., Wong, J., Hurst, J., MacVane, S.
American Society of Health-System Pharmacists - 2018

Purpose

The implementation and optimization of molecular rapid diagnostic tests (mRDTs) as an antimicrobial stewardship intervention for patients with bloodstream infections (BSIs) are reviewed.

Summary

All U.S. acute care hospitals accredited by the Joint Commission are required to implement an antimicrobial stewardship program (ASP). Of the many interventions available to ASPs, mRDTs have demonstrated consistent, meaningful results on antimicrobial optimization and patient outcomes. Even among infectious diseases and antimicrobial stewardship–trained pharmacists, significant knowledge and familiarity gaps exist regarding available mRDTs and how best to implement and optimize them. Given the paucity of infectious diseases and/or antimicrobial stewardship–trained pharmacists, the mandates for establishing ASPs will require non-infectious diseases/antimicrobial stewardship–trained pharmacists to implement stewardship interventions, which may include mRDTs, within their institution. Optimization of mRDTs requires adequate diagnostic stewardship, specifically evaluating how mRDT implementation may decrease costs and assist in meeting antimicrobial stewardship regulatory requirements. Knowledge of how these technologies will augment existing microbiology and antimicrobial stewardship workflow is essential. Finally, selecting the right mRDT necessitates familiarity with the instrument's capabilities and with the institutional antibiogram.

Conclusions

mRDTs have demonstrated the ability to be one of the most powerful antimicrobial stewardship interventions. Pharmacists required to implement an ASP in their institution should consider mRDTs as standard of care for patients with BSIs.

Rapid Blood Culture Identification: A Lower Cost Per Panel Might Equal a Higher Cost for the Laboratory

GenMark Diagnostics - 2018

Abstract

The development of rapid blood culture identification (BCID) has set the stage for significant strides in improving patient care. This includes the laboratory's ability to directly impact the quality measures that were recently established within the healthcare community, including reducing infection and readmission rates, improving antibiotic stewardship, the quality of care and patient experience[1]. Microbiology laboratories are faced with selecting the appropriate molecular assay for their institution and building the business case to justify the incremental costs that can sometimes accompany a technology transition or upgrade. Without a full assessment of the laboratory and overall hospital costs that could be incurred or avoided, assay selection might be based solely on the cost per test. It is necessary to consider all aspects of assay design and performance when considering adopting a new technology or test. This white paper evaluates the ePlex BCID benefits that provide overall cost advantages compared to other commercially available rapid BCID assays.

Traditional methods of identification can take an average of 24 – 72 hours from the time the blood culture bottle flags positive. In the case of fastidious organisms like facultative anaerobes, an identification can take up to 5 days after bottle positivity. This could result in the patient being exposed to unnecessary or inappropriate antibiotics for a prolonged amount of time; and inappropriate antimicrobial use can carry a heavy financial burden for the hospital and a substantial hardship for the patient[2,3].

The ePlex System is the only rapid blood culture identification solution that detects and identifies anaerobic bacteria. This provides a cost savings for the laboratory greater than $50 per culture - as additional testing is no longer needed for organism identification. In addition to the cost savings for the laboratory, the physician can optimize therapy less than two hours after bottle positivity.

Contamination rule-out targets help eliminate the need for unnecessary identification of non-pathogenic organisms and can save the laboratory an average of $34.69 per culture. Additionally, detecting contaminants early can reduce the use of unnecessary antibiotics and decrease hospital length of stay which can also reduce the adverse effects of and costs associated with empiric antimicrobial therapy[2].

For complete white paper, visit: www.genmarkdx.com.

1. https://www.cms.gov/Medicare/quality-initiatives-patient-assessment-instruments/qualitymeasures/index.html
2. Antibiotic Resistance Threats in the United States, 2013. U.S. Dept. of Health & Human Services, Centers for Disease Control and Prevention
3. Wenzler, E., et. al., (2016), Antibiotics, 5(1), 6

Enabling Rapid Care Decisions

Diagnosing sepsis can be frustratingly slow when traditional techniques are employed, lives can be saved by speeding up the process. *Practical Patient Care* talks to Dr Natalie Whitfield, director of scientific and medical affairs at **GenMark Diagnostics**, about how ePlex technology is improving patient care.

Can you provide background on GenMark Diagnostics and the ePlex system?

Dr Natalie Whitfield: GenMark Diagnostics delivers molecular diagnostic solutions, designed to impact patient outcomes and reduce cost-of-care. The ePlex system integrates the entire process from order-to-report, and offers unique solutions designed to improve antimicrobial stewardship (AMS) and infection control in the delivery of patient-centred, value-based care. The ePlex software provides bidirectional LIS, epidemiological tracking, auto-filing of results, external quality control management and the new Templated Comments (TC) module.

How does the Templated Comments module work?

The availability of rapid, multiplexed technologies for comprehensive detection of infectious diseases is creating a paradigm shift in the role labs play in impacting patient outcomes, infection control and AMS. The drastically improved turnaround time from test order to reported result removes the laboratory as a bottle neck in patient care. The new capability has created the need for enhanced synergy between the lab and the rest of the care team.

The ePlex TC module provides a rules-based engine that enables users to customise conditions based on the ePlex Blood Culture Identification (BCID) Panel results to communicate interpretive comments on the result report and through to the LIS. Users can define specific rules for organism and antimicrobial resistance gene combinations in a logical structure. The TC module allows pharmacists to translate the antibiogram, formulary and their expertise into an action plan, empowering physicians to more quickly and efficiently treat patients and improve patient care.

Could you run through a case study of how it might be used in practice?

A patient arrives at the ED with suspected sepsis. Blood culture bottles are collected while the patient is started on broad spectrum antibiotics. Blood bottles ring positive later that day, triggering pathogen ID and resistance testing. Using the ePlex system, pathogen ID and antimicrobial resistance gene results are available within 90 minutes. Alternatively, traditional subculture and AST results take 48 hours.

If the laboratory has implemented the ePlex TC module, customised results can be transmitted from the instrument into the LIS, providing guidance on how to use these rapid results, eliminating the need to wait for consulation from specialists.

ePlex delivers solutions for lab workflow, safety and data management.

How does your ePlex system benefit laboratories, patients and clinicians?

Laboratories benefit from an easy-to-use system, that can be performed on all shifts. The test requires less than two minutes of hands-on time and the results can be automatically released to the LIS. Clinicians benefit from rapid results that can provide institution-specific guidance for optimal treatment.

The ePlex system has the broadest BCID panels available, delivering more information faster than non-molecular identification methods and AST so clinicians can make treatment decisions days earlier than for AST results, potentially improving outcomes.

In general, how does this approach distinguish GenMark in the market?

Recent studies have shown that rapid results for bloodstream infections have a significant impact on patients and the cost of care when the results are combined with an AMS.

The bidirectional interface, from order-to-report, with new customized Templated Comments helps hospitals provide quality patient care and keep compliance with their AMS metrics.

Improved Diagnostics

Designed for the patient and optimised for the lab, **GenMark Diagnostics'** new ePlex system is the first truly integrated sample-to-answer solution for clinical diagnostics. Dr Julie A Ribes and Dr Vaneet Arora, directors of clinical microbiology at University of Kentucky HealthCare, an associated hospital system in Lexington, have recently tested the system, and they share their conclusions with us.

What benefits have you found from using ePlex blood culture identification panels over traditional diagnostic methods?

Dr Julie A Ribes: The ePlex panels have superior inclusivity compared with the panel we are currently phasing out. The gram-negative (GN) coverage is particularly outstanding. During our head-to-head comparison of ePlex to our current blood culture identification (BCID) system, there was more than a 30% increase in pathogen detection. The ePlex detected 43 true positive results compared to only 29 by our other method. For the gram-positive (GP) panel, ePlex detected an additional 13 true positive results above our current method, for an increase of 9% in rapid detection.

UK Healthcare caters to a large intravenous drug-using population, and we have a relatively large number of patients with unusual organisms in their blood as a result. During our evaluation, we had three *Serratia* spp, three *Stenotrophomonas maltophilia*, one *Morganella morganii*, and even a *Fusobacterium necrophorum* detected by the ePlex and culture, but not by the rapid microarray method. Historically, our pharmacy doctors (PharmDs) have requested more rapid identification for *Serratia* spp and have asked us to perform additional molecular testing if a gram-negative organism was seen on gram stain, but not identified by our primary BCID. The ePlex will take away this redundant testing and delay in turn-around-time for detection.

The ePlex pan-gram-negative and pan-gram-positive analyses are also helpful. We had several instances where these were positive, but the gram-stain morphology had not been recognised initially, particularly with mixed cultures.

Can you describe the ePlex user experience? How does it help to prevent errors and ensure patient safety?

Dr Vaneet Arora: The ePlex system is true walk-away technology with an intuitive process. First, the positive blood culture bottle is processed under the biological safety cabinet to remove an aliquot to a labelled tube, prepare the gram stain and plate the cultures. The appropriate ePlex panel is then selected based on the gram-stain characteristics of the organisms seen. Patient and specimen identification are barcode driven, so the test results are linked to the specific patient being tested. The cartridge is scanned for definitive patient and panel identification, and is then inserted into the instrument, and the tech walks away as testing proceeds. The instrument's interface allows for the test results to be uploaded directly for reporting into the electronic medical record.

Our current instrument has several phases of testing, and resulting is all manual. This has been a significant cause of error over time and is another major reason why we are replacing the current platform.

How does ePlex compare with or fit in with your organisation's standard of care methodologies? Has it impacted how you think about standard of care for blood sampling and diagnosis?

VA: Our PharmDs are clamouring for a more comprehensive panel for reporting blood culture results. Our current panel was brought in with the understanding that all molecular blood culture results would be reported to a PharmD 24/7 so that antimicrobial administration could be optimised to better support patient care. The ePlex system with its more extensive coverage will allow for a more robust intervention, especially for GNs like *Serratia* and *Stenotrophomonas*, which we see so commonly in our patients. The Fungal Panel – which we are still evaluating – also promises to be an excellent addition to our current testing platform, which is quite limited in comparison.

How has ePlex improved or aided your antimicrobial stewardship efforts?

VA: UK HealthCare is already at the cutting edge of antimicrobial stewardship. Having the ePlex panels will better allow our PharmDs and the clinical care teams to manage patients, and to either escalate or de-escalate antimicrobials more efficiently. This is the ultimate goal in switching platforms.

In our evaluation, the ePlex results would have decreased turnaround times by 24 hours for antimicrobial optimisation in at least eight patients using the gram-negative panel. We are anxious to make this switch to ePlex for rapid BCID testing.

Comprehensive Coverage of Pathogens and Resistance Genes

ePlex® BCID-GP Panel	ePlex® BCID-GN Panel	ePlex® BCID-FP Panel
Gram-Positive Organisms	**Gram-Negative Organisms**	**Fungal Organisms**
Bacillus cereus group	*Acinetobacter baumannii*	*Candida albicans*
Bacillus subtilis group	*Bacteroides fragilis*	*Candida auris*
Corynebacterium	*Citrobacter*	*Candida dubliniensis*
Cutibacterium acnes	*Cronobacter sakazakii*	*Candida famata*
(Propionibacterium acnes)	*Enterobacter (non-cloacae* complex*)*	*Candida glabrata*
Enterococcus	*Enterobacter cloacae* complex	*Candida guilliermondii*
Enterococcus faecalis	*Escherichia coli*	*Candida kefyr*
Enterococcus faecium	*Fusobacterium nucleatum*	*Candida krusei*
Lactobacillus	*Fusobacterium necrophorum*	*Candida lusitaniae*
Listeria	*Haemophilus influenzae*	*Candida parapsilosis*
Listeria monocytogenes	*Klebsiella oxytoca*	*Candida tropicalis*
Micrococcus	*Klebsiella pneumoniae*	*Cryptococcus gattii*
Staphylococcus	*Morganella morganii*	*Cryptococcus neoformans*
Staphylococcus aureus	*Neisseria meningitidis*	*Fusarium*
Staphylococcus epidermidis	*Proteus*	*Rhodotorula*
Staphylococcus lugdunensis	*Proteus mirabilis*	
Streptococcus	*Pseudomonas aeruginosa*	
Streptococcus agalactiae (GBS)	*Salmonella*	
Streptococcus anginosus group	*Serratia*	
Streptococcus pneumoniae	*Serratia marcescens*	
Streptococcus pyogenes (GAS)	*Stenotrophomonas maltophilia*	
Resistance Genes	**Resistance Genes**	
mecA	CTX-M	
mecC	IMP	
vanA	KPC	
vanB	NDM	
	OXA	
	VIM	
Pan Targets	**Pan Targets**	
Pan Gram-Negative	Pan Gram-Positive	
Pan *Candida*	Pan *Candida*	

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GNMK-IMC-7165-A