Advances and Trends in Sepsis Diagnostics

Mark D. Hughes, Vice President, mhughes@eacorp.com
Enterprise Analysis Corporation

Abstract

There is a compelling need for a rapid sepsis diagnostic test or suite of tests. Over the last decade at least 25 IVD companies have introduced or are in the process of developing diagnostic products to reduce the time to diagnosis of sepsis, identify pathogens and profile antibiotic susceptibility. This article provides a review of the current state of sepsis testing and the companies that are active in this arena.

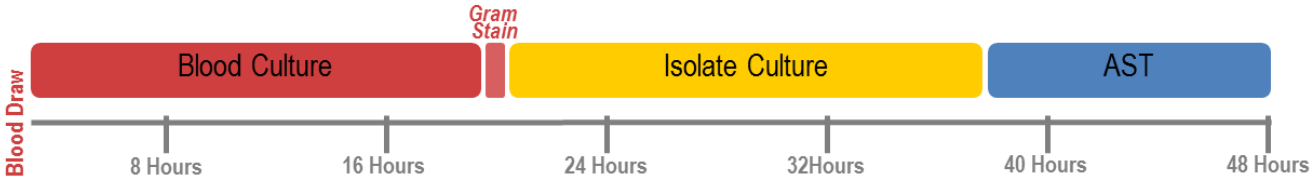
Background

Sepsis, often referred to as septicemia, is the body's immune response to a life-threatening blood stream infection. In the US, there are an estimated 1.7 million cases of sepsis each year and more than 265,000 deaths.[i] According to the Agency for Healthcare Quality and Research, the healthcare costs incurred from sepsis in 2013 reached nearly $24 billion, roughly 6% of the nation's hospital bill, while these sepsis patients represented only 3.6% of all hospital stays.[ii]

The lack of a reliable, rapid diagnostic test for sepsis has forced clinicians to treat suspected sepsis cases empirically with high dose, broad spectrum antibiotics. In fact, the mortality rate for sepsis increases by 7.6% with each hour of treatment delay.[iii] This leads to treatment decisions based primarily on clinical presentation and physiological parameters (e.g. temperature, heart rate and respiration) along with basic non-specific laboratory tests such as complete blood count, C-reactive protein (CRP), blood lactate and procalcitonin.

The traditional blood culture is the current "gold standard" for sepsis diagnosis. It is clearly an imperfect standard as there are numerous false negative blood cultures and only about 10% of blood cultures are positive for a pathogen, according to EAC's observations. In fact, it is well known that blood cultures are frequently negative when all other tests and clinical signs point to sepsis. Further complicating the issue is the fact that blood cultures typically take 16-24 hours before turning positive. Nonetheless, it is still the mainstay of diagnosis.

Generally speaking, if a blood culture turns positive (i.e. bacterial or fungal growth), that positive blood culture is examined using a Gram stain so that a preliminary result can be provided to the clinician as Gram-positive, Gram-negative bacteria, or fungal growth. Next, a subculture is performed on plated culture media which takes another 1-2 days to grow. The suspect colony on the culture media is identified using phenotypic biochemical identification methods or mass spectrometry. Finally, antibiotic susceptibility testing (AST) is performed to determine which antibiotics the isolated pathogen is sensitive to. Thus, the entire diagnostic process takes 48-96 hours on average.



The Unmet Need

Given the long time frame for obtaining culture results, there is an obvious unmet need for fast and accurate laboratory tests for sepsis. This need is especially critical in an age where antibiotic drug resistance is becoming more common and the arsenal of effective antibiotics available to treat these resistant infections is limited. Empiric antibiotic therapy which results in ineffective treatment can contribute to the rise in antibiotic resistant strains. As a result, hospitals are increasingly being encouraged to practice careful "antibiotic stewardship" in order to prevent expansion of antibiotic resistance strains. In the absence of a firm diagnosis, pathogen identification and antibiotic susceptibility profile, it is difficult for the clinician to choose the best antibiotic therapy at the onset of treatment. There are both strong clinical and health economic cases to be made for rapid sepsis diagnosis, as it can translate into better treatment decisions leading to improved patient outcomes and reduced hospitalization costs.

To summarize, the unmet need for an ideal, *holy grail* sepsis test (or panel) can best be described as:

1. A rapid, 1 hour "yes/no" sepsis test to reliably rule in or rule out sepsis.
    - Ruling out sepsis with a high negative predictive value (NPV) would prevent clinicians from starting unwarranted and expensive antibiotic therapy. This might be a simple immune "host-response" assay.
2. In the case of a positive sepsis test, a second rapid test, preferably within 3 hours of suspicion, that provides the pathogen identification, or, at a minimum a Gram-positive vs. Gram-negative vs. fungi test result.
    - This allows the clinician to narrow the antibiotic therapy regimen, reduce unnecessary doses and discharge patients from the hospital earlier all of which can lower risk of adverse side effects and lower overall costs.
    - This is a significant challenge because the breadth of causative organisms is enormous; 25–30 organisms account for the majority of sepsis, but that still leaves a very long list of organisms that occasionally result in sepsis.
3. A third test that provides a rapid antibiotic susceptibility profile, ideally within 1-2 hours; but 6 hours after initiation of antibiotics may be acceptable.
    - This allows the clinician to optimize the choice of antibiotic and the dosage.
    - Ideally the diagnostic tool helps provide the best antibiotic and amount from the first dose, but as a fall back, at least being able to make an effective change by the second dose (usually 4 – 8 hours later) is a good option.

Interestingly, many of the infectious disease physicians EAC has spoken with, would argue that simply telling them the antibiotic susceptibility profile of the pathogen is more important than knowing the identification of the pathogen itself.

Today's tool set is diverse and incomplete so each physician marries his/her individual experience with the biomarkers, algorithms and related information to move as quickly as possible in treatment decisions. This has resulted in standards of care that are still in flux and best practice is debated regularly. A comprehensive and effective diagnostic would be a significant advance in medicine.

Sepsis Diagnostic Products

In response to the unmet need described above, a variety of new laboratory tests have been brought to market or are still in development. These can be divided into 3 broad categories:

1. Tests for rapid identification of pathogens from a positive blood culture.
2. Tests to identify pathogens directly from a blood sample in 1-6 hours.
3. Tests to rule in or rule out sepsis by detection of specific blood biomarkers, host-immune system response, or white blood cell morphology characteristics.

Each of these categories of tests is discussed in more detail below.

Rapid Identification from Positive Blood Culture

Over the past decade, several diagnostic test products have been introduced that allow for the rapid identification (ID) of pathogens direct from positive blood cultures. For example, several IVD manufacturers have introduced rapid "sample-to-answer" molecular tests that allow the microbiologist to identify the organism(s) in the positive blood culture in 1-2 hours (Table 1). The benefit of this type of rapid result is that it allows the clinician to make an earlier decision regarding escalation or de-escalation of antibiotic therapy. While these tests are not the ideal "direct from whole blood" sepsis test, they do represent a step in the direction of faster, more accurate diagnosis.

bioMérieux/BioFire

France based bioMérieux (Marcy l 'Etoile, France), which acquired US based BioFire (Salt Lake City, UT) in 2014, received FDA approval in 2013 for a blood culture ID test for its FilmArray system. The FilmArray Blood Culture test is a simple "sample-to-answer" multiplex real-time PCR based test that detects 24 pathogens and 3 antibiotic resistance markers from a positive blood culture bottle. Results are available in approximately 1 hour.

Luminex and GenMark Diagnostics

Similarly, two other companies, Luminex (Austin, TX) and GenMark (Carlsbad, CA) have blood culture ID tests with results in 1.5-2 hours. The Luminex Verigene test provides the flexibility of testing for either Gram-negative or Gram-positive bacteria, in separate test cartridges. The GenMark blood culture assay is available outside the US with separate panels for Gram-positive, Gram-negative and fungal pathogens. The Gram-negative panel, for example, detects 21 different bacteria and 6 antibiotic resistance genes.

Mobidiag

Mobidiag (Espoo, Finland) actually introduced the first blood culture pathogen ID test in 2008 with its Prove-it Sepsis test. The product requires a separate DNA extraction step followed by standard PCR amplification and then detection on a DNA array that detects 84 bacteria, fungi and antibiotic resistance markers in 3 hours. This was a "first generation" sepsis test and it appears that the company has halted sales of this product.

In May 2018, the company announced new investor funding of $1.74 million for development of a next generation rapid sepsis test on its new Novodiag sample-to-answer instrument platform aimed at producing results within approximately 1 hour.

Cepheid and BD

Two other key players in this space are Cepheid (Sunnyvale, CA) and BD (Franklin Lakes, NJ). Cepheid has a 1 hour sample-to-answer test on its GeneXpert system for detection of *Staphylococcus aureus*. The test is specifically designed to detect methicillin-sensitive *Staph aureus* (MSSA) and methicillin-resistant *Staph aureus* (MRSA) direct from Gram-positive blood cultures. This test has been on the market now for many years and is useful when there is high suspicion of *Staph aureus* from the Gram stain. Similarly, BD has the StaphSR test available on it BD Max instrument for detection of *Staph aureus* and MRSA from positive blood cultures with results in about 2 hours.

Accelerate Diagnostics

Accelerate Diagnostics (Tucson, AZ) has introduced the Pheno system which identifies pathogens from positive blood cultures in 1.5 hours using a molecular method called fluorescent in-situ hybridization (FISH). The Pheno system also performs antimicrobial susceptibility testing (AST) on the identified organism using time lapse imaging of bacteria and computer algorithms with results in 6 to 7 hours. The company received FDA approval in February 2017 and has already achieved revenues of more than $4 million in 2017, along with more than 300 contracts for instruments. This suggests that the product is gaining acceptance in the market.

Emerging Companies

Momentum Bioscience (Cardiff, Wales), is taking a slightly different approach to sepsis. Instead of identifying the pathogen present in the blood culture, it is ruling out all the negative blood cultures in one day, thereby, allowing physicians to stop or de-escalate empiric antibiotic therapy. This saves money, is safer for the patient and reduces antibiotic resistance.

The technology called Enzymatic Template Generation and Amplification (ETGA) amplifies only viable microbial cells. This is a qPCR based procedure performed on blood cultures at 12-24 hours that show no growth yet. Clinical studies so far indicate that it can reliably rule out negative blood cultures with a 99.5% NPV. In other words the test can determine which patients are *not* bacteremic and those blood cultures with a negative test result can lead to discontinuation of antibiotics.

At least two other molecular diagnostic companies have been developing multiplex blood culture ID tests as well. A small company named iCubate (Huntsville, AL) obtained FDA approval for a multiplex Gram-positive ID test in 2017 and is awaiting approval for a separate Gram-negative ID test.

Another start-up company, Finland based Abacus Diagnostica is commercializing its GenomEra PCR platform which includes a blood culture identification test for *Staph aureus* and *Streptococcus pneumoniae.*

Yet another approach to rapid identification of bacteria and fungi in positive blood cultures is a form of mass spectrometry called MALDI-TOF. This technology is being used by some microbiology laboratories in the form of a Laboratory Developed Test (LDT), an assay developed by a lab for internal use, as there are currently no FDA approved tests available using MALDI-TOF for this particular indication. The key advantage is that it produces very rapid results at a very low cost per test (once the instrument has been paid for). MALDI-TOF can also be used to detect some antibiotic resistance markers.

Two companies supply MALDI-TOF equipment to microbiology laboratories and are actively working in this area, Bruker Daltonics (Billerica, MA) with its Biotyper instrument and bioMérieux with its Vitek MS system.

Molecular Pathogen Identification Tests Direct From Blood Sample

At least five companies have already introduced molecular based tests for pathogen identification direct from a whole blood sample. Three of these tests have been available for sale outside the US for many years. A fourth company, T2 Biosystems, received CE Mark for a direct from blood sepsis panel in July, 2017 and FDA approval on May 29, 2018. Yet another company, Karius began offering an NGS based testing service for sepsis through its own CLIA certified laboratory in 2017 as well.

EAC believes that the original first generation direct blood assays are not well-suited for “on demand” testing as currently configured. In addition, the relative assay sensitivity, and/or time to result remains a concern among laboratories that have evaluated these tests, making it difficult to justify the cost of the assays.

EAC’s field checks with laboratories indicate that these tests have not yet been broadly adopted in microbiology laboratories, although the T2 Biosystems assays are finally gaining some traction in the market.

Roche Molecular

The Roche Molecular SeptiFast PCR test kit was first introduced in 2006 with CE-IVD approval outside the US. The test is performed on the LightCycler 2.0 instrument and can detect 25 different bacteria and fungi that account for over 95% of blood stream infections.

The SeptiFast test is designed to be used in conjunction with standard microbiology procedures and clinical presentation. Test results take 4-6 hours including the time for nucleic acid extraction. The LightCycler is a batch instrument and is, therefore, not ideal for running one sample at a time on demand which reduces the positive impact this test could have.

More recently, in 2015, Roche Molecular Systems acquired US based GeneWeave technologies for $190 million with additional payments of up to $450 million total if GeneWeave meets all its development milestones.

GeneWeave has been developing a fully automated platform using a proprietary "Smarticle" technology for AST testing. Simply put, these are DNA delivered bio-particles that enter bacterial cells and cause live bacteria to produce luciferase, thereby allowing phenotypic detection to an antibiotic in 3-4 hours. A bioluminescent signal is detected by the instrument. The initial commercial focus seems to be AST but the technology appears capable of performing pathogen identification as well.

Molzym

Molzym GmbH (Bremen, Germany) introduced a CE Mark direct from blood sepsis test called SepsiTest in 2008. It can detect more than 345 different genus and species of bacteria and fungi from 1ml of whole blood. It is intended for use with other standard diagnostic tests. After the DNA purification and PCR steps the assay requires gel electrophoresis followed by confirmatory sequencing analysis for the pathogens detected.

While interesting, the assay configuration is very hands on and basically requires 4 or more hours to run and, therefore, it is not very practical for "on demand" testing in most routine microbiology laboratories.

Seegene

Seegene (Seoul, South Korea) has a direct from whole blood multiplex PCR pathogen identification test on the market outside the US. The test, called Magicplex, detects 90 different bacterial and fungal species including 3 drug resistance markers. Test results are available in approximately 3 hours (excluding sample preparation and DNA extraction time). The assay can be run on several "open" real-time PCR instruments such as the Bio-Rad CFX96 and the Thermo AB7500. The company is currently working with various partner companies to deliver a more automated assay format for many of its assays.

T2 Biosystems

T2 Biosystems (Lexington, MA) is the newest entry into the sepsis market. The company uses proprietary magnetic resonance technology along with superparamagnetic particles that are coated with pathogen specific binding agents.

T2 has already obtained FDA approval in September 2014 for its T2Candida panel, a direct test for Candida species from whole blood with results in 3-5 hours. The company claims that the test is 91% sensitive and can detect as few as 1 CFU/ml of Candida in a blood sample.

In July 2017, T2 obtained CE Mark for its bacterial sepsis panel called T2Bacteria and on May 29, 2018, it received FDA approval for this panel. This test detects six of the most serious sepsis causing Gram-negative and Gram-positive bacterial species with results in 3-5 hours.

It is worth noting that with all of the aforementioned pathogen ID tests, a blood culture isolate is still needed to perform AST in order to optimize antibiotic therapy. The only exception is the Accelerate Diagnostics PhenoTest that performs both ID and AST from the positive blood culture.

Karius

Karius (Redwood City, CA) is a new entrant in the sepsis testing market. The company operates a licensed CLIA certified laboratory and uses Next Generation Sequencing (NGS) to detect cell free microbial DNA (cfDNA) from a 5 ml plasma sample.

The company claims to detect more than 1,000 different bacteria, viruses, fungi and parasites from a blood sample with results available in 1 day (from blood sample receipt at the lab).

In a study published in 2017 in the journal Open Forum Infectious Diseases, the authors (who are company employees) claim that the NGS test detected pathogens in septic patients three times more often than blood culture. In another study described on the Karius website, 350 suspected sepsis patients were tested by NGS and traditional blood culture. The company claimed to have 93% sensitivity versus blood culture.

This test may prove especially valuable in patients whose blood contains pathogens that are difficult to grow in culture (e.g. *Bartonella* species) and for patients with Fever of Unknown Origin.

Beyond these five companies, there are several others that are working to develop direct from blood pathogen identification tests for sepsis. Among these are PathoQuest, Q-linea AB, DNAe, and Qvella.

PathoQuest

France based PathoQuest, founded in 2010 as a spinoff of the Pasteur Institute, is developing a direct from blood sepsis assay called iDTECT. The test utilizes NGS to identify more than 1,200 viral and bacterial pathogens from a 5 milliliter blood sample. This test has already obtained the CE Mark in Europe where it is offered through a PathoQuest laboratory and is specifically aimed at the immunocompromised patient population. Test results take about 2 days. Eventually, PathoQuest plans to offer the test in the US market as a laboratory developed test (LDT) through different partner laboratories.

The company has raised €6.7 million in seed financing and is looking to raise additional capital in a Series B financing round.

Q-linea

Q-linea AB (Uppsala, Sweden) is a development stage company founded in 2008 that is focused on developing a rapid pathogen ID and AST system direct from the patient blood sample.

The Q-linea technology is based on a molecular amplification method called circle-to-circle isothermal nucleic acid amplification (C2CA). The company has developed a prototype instrument platform called the ASTrID that provides a 4 hour pathogen identification direct from whole blood and covers

33 different pathogens and 11 antibiotic resistance markers. In addition, the system will then perform a phenotypic AST covering 48 antibiotics with a result at 10 hours after test initiation.

Qvella

Yet another company entering the sepsis testing space is Qvella (Ontario, Canada). Qvella is developing a rapid, multiplex PCR assay system called FAST-ID. This is a "sample-to-answer" PCR system that is intended to deliver a pathogen ID result in about 1 hour from a blood draw. It features closed tube blood sampling, disposable test cartridges, two minutes of hands on time and automated concentration and lysis of bacterial pathogens.

The company raised $20 million in Series B financing in the fall of 2017. Product development continues but a product launch date has not been announced.

DNAe

London based DNAe has developed a system for blood stream infections called LiDia. The company has presented poster sessions at recent microbiology and molecular meetings claiming that it can detect pathogens in blood in concentrations as low as 1 CFU/ml. The LiDia is a closed system that performs the DNA extraction and a nested PCR pre-amplification in a self-contained test cartridge. According to their website, any DNA or RNA from a pathogen can be detected using standard semiconductor technology. Simply put, hydrogen ions that are released during DNA/RNA sequencing or amplification are detected by electrical signal using a complementary metal oxide semiconducter (CMOS) chip. The company claims that test results, including AST, can be determined in 3 hours.

Host Response and Biomarker Detection Direct From Blood (No Pathogen ID)

Rather than using direct pathogen identification approaches, some other IVD companies are taking different approaches to sepsis testing, such as detecting host immune response or various blood-based biomarkers. Some of these tests are now commercially available while others are still in the development stage.

Over the last 10 years, procalcitonin (PCT) immunoassays have gained widespread use as a biomarker test that is useful in diagnosing, monitoring and tailoring treatment for patients with sepsis. Several IVD vendors now offer PCT assays on automated immunoassay platforms (e.g. Abbott Architect, Beckman AU series) and others are reported to be developing point-of-care versions of the PCT test. However, PCT is not an ideal sepsis diagnostic and it does not eliminate the need for blood culture and antimicrobial susceptibility testing or other indicator tests of sepsis.

Immunexpress

One company in particular, Immunexpress (Seattle, WA), has been working toward a direct from blood rapid sepsis test for many years. In February 2017 Immunexpress received FDA 510(k) approval for the SeptiCyte test as an aid in differentiating patients that have actual sepsis from patients that have a systemic inflammation condition called systemic inflammatory response syndrome (SIRS).

The Immunexpress SeptiCyte test is an RNA-based qPCR test that looks at a patient's own immune response to infection by measuring the expression of four genes involved in the immune inflammatory response.

The SeptiCyte test uses a 2.5 ml sample of blood and is approved for use with the Thermo Fisher AB 7500 Fast Dx PCR analyzer. Time to results is in the range of 3.5 to 5 hours including sample RNA extraction.

In January 2018, Immunexpress announced a collaboration with Belgium-based Biocartis to put the SeptiCyte host response sepsis test on the Biocartis Idylla point-of-care platform. Idylla is a fully integrated "sample-to-answer" platform that can produce test results in 1-2 hours.

Beckman Coulter

Beckman Coulter (Brea, CA), a subsidiary of Danaher and a longtime market leader in hematology testing, announced in May 2018 that it had received CE Mark for its Early Sepsis Indicator test. This test examines morphological characteristics of monocytes as part of a standard complete blood count (CBC) and differential. The change in the morphology of the monocytes is a potential indicator of sepsis. According to the press release, the test serves as an important tool for emergency department doctors to detect early sepsis or the risk of developing sepsis. The company says that it will submit a 510(k) application to the FDA in the near future.

Abionic

Abionic SA (Lausanne, Switzerland), founded in 2010, has developed a nanotechnology based point-of-care platform called the abioSCOPE. The abioSCOPE is a small, touchscreen, portable desktop instrument that uses a miniaturized fluorescence microscope for detection. The test cartridge, called IVD Capsule, requires application of a 50 µl sample of whole blood and yields test results in 5 minutes.

In 2017, the company received CE Mark for a proprietary sepsis test called pancreatic stone protein (PSP) test. The clinical studies to date indicate that the PSP test can help to identify sepsis patients at an early stage in the ICU and emergency department. Commercial launch of the product is expected in late 2018, according to company press releases.

Cytovale

Cytovale (San Francisco, CA) is a start-up company developing a sepsis test on a microfluidic platform that examines structural changes to white blood cells when dysregulation of the immune system occurs. The first application for the technology is a rapid test for sepsis for use in the emergency department.

Inflammatix

Another company developing a host response immune assay is Burlingame, CA based start-up Inflammatix. The company, founded in 2016, is developing an 18 gene host response molecular assay called HostDx Sepsis that can presumably distinguish bacterial from viral infection in suspected sepsis

patients as well as stratify patients based on severity and assess 30-day mortality. This test is still in the development stage and it will likely be two years or more before it gains regulatory approval.

Sphingotec

Sphingotec GmbH (Henningsdorf, Germany) was founded in 2002 with the mission of discovering new biomarkers for disease. The company has developed a new immunoassay test, bio-ADM, which measures a biomarker called adrenomedullin, a peptide hormone that is involved in regulating vasodilation and vascular leakage of blood vessels. As such, it can be used in the prediction and diagnosis of septic shock and to support clinical decisions to give vasopressor therapy. A rise in the blood level of bio-ADM usually occurs prior to the onset of septic shock.

The company recently announced a collaboration with US based Nexus Dx (San Diego, CA) to develop its assays for use on the Nexus Dx IB-10 microfluidic POC instrument. This instrument can produce immunoassay results at the point-of-care in as little as 20 minutes.

Conclusion

Significant advances have been made in sepsis testing in recent years. EAC believes that the ideal sepsis diagnostic will require a suite of different tests, most likely involving a combination of a rapid "host response" immune test, biomarkers that can be used for tracking progression or remission of the disease and rapid pathogen identification coupled with rapid antibiotic resistance testing. A multi-billion dollar market opportunity awaits for companies that can deliver rapid, accurate sepsis tests. Given recent progress in this field, it appears that the IVD industry is on the verge of finally achieving this goal.

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Table 1:

Company	Product or Platform	Status	Technology	Time to Result (approx.)	Specimen Type	Pathogen ID	Genetic Resistance Markers	Full AST	Host Response	Biomarker/ Other
BioFire	FilmArray	On Market	RT-PCR	1 hour	Blood culture	Yes	Yes	No	No	No
Luminex	Verigene	On Market	Gold nanoparticle microarray	2 hours	Blood culture	Yes	Yes	No	No	No
GenMark	ePlex	On Market	PCR	1.5 hours	Blood culture	Yes	Yes	No	No	No
Accelerate Diagnostics	PhenoTest	On Market	FISH	1.5 hours (ID); 6-7 hours (AST)	Blood culture	Yes	No	Yes	No	No
Cepheid	Xpert SA/MRSA	On Market	RT-PCR	1 hour	Blood culture	Yes	Yes (MRSA)	No	No	No
BD	StaphSR	On Market	RT-PCR	2 hours	Blood culture	Yes	Yes (MRSA)	No	No	No
Mobidiag	Prove-it	On Market	PCR	3 hours	Blood culture	Yes	Yes	No	No	N0
iCubate	iC-System	On Market	ARM-PCR	3-4 hours	Blood culture	Yes	Yes	No	No	No
Abacus Diagnostica	GenomEra	Development	RT-PCR	1 hour	Blood culture	Yes	Yes	No	No	No
Momentum Bioscience	Cognitor Minus	Development	EGTA	12-24 hours	Blood culture	Confirms negatives	No	No	No	No
Roche Molecular	SeptiFast	On Market	RT-PCR	4-6 hours	Whole blood	Yes	Yes	No	No	No
Roche GeneWeave	Smarticle	Development	DNA bioparticles	3-4 hours	Whole blood	Yes	No	Yes	No	No
Seegene	Magicplex	On Market	RT-PCR	3-4 hours	Whole blood	Yes	Yes	No	No	No
Molzym	SepsiTest	On Market	PCR	4-5 hours	Whole blood	Yes	Yes	No	No	No
T2 Biosystems	T2Bacteria	On Market	Magnetic Resonance	3-5 hours	Whole blood	Yes	No	No	No	No
Immunexpress	SeptiCyte	On Market	Gene expression	3.5-5 hours	Whole blood	No	No	No	Yes	No
Karius	Karius Test	On Market	NGS	>24 hours	Whole blood	Yes	No	No	No	No
PathoQuest	iDtect	On Market	NGS	48 hours	Whole blood	Yes	Yes	No	No	No
Q-linea	ASTrID	Development	Rolling Circle Isothermal Amp.	4 hours for ID; 10 hours AST	Whole blood	Yes	Yes	Yes	No	No
Qvella	FAST-ID BSI	Development	Multiplex PCR	<1 hour	Whole blood	Yes	Yes	No	No	No
DNAe	LiDia	Development	PCR and semi-conductor chip	3 hours	Whole blood	Yes	Yes	Yes	No	No
Inflammatix	HostDx Sepsis	Development	Gene expression profile	N/A	Whole blood	No	No	No	Yes	No
Cytovale	NA	Development	White Blood Cell morphology	<10 minutes	Whole blood	No	No	No	No	Yes
Abionic	abioSCOPE	Development	PSP Biomarker - Immunoassay	5 minutes	Whole blood	No	No	No	No	Yes
Sphingotec	Nexus IB10	Development	Bio-ADM-Immunoassay	20 minutes	Whole blood	No	No	No	No	Yes
Beckman Coulter	DxH 900	FDA filing (510k)	Monocyte morphology	<5 Minutes	Whole blood	No	No	No	No	Yes

About EAC

EAC is a strategic healthcare consulting company that provides business development and research services to technology developers in both the *in vitro* and *in vivo* domains, as well as to life science enterprises and pharmaceutical companies.

In our 30 years of operation, we have delivered over 1400 projects to 160 client companies serving the US, Europe, Japan, China, Brazil, and other markets of the world. We have expertise across the spectrum of diagnostic technologies, disease and wellness states, and healthcare delivery settings in both human and animal health.

We conduct clinical studies, both retrospective and prospective, to determine the intrinsic value of a new diagnostic test. This valuation estimates outcomes improvements, cost savings, and quality of care improvements that a new technology could deliver. In the past ten years we have carried out such studies for a new cardiac marker, a set of markers that could advance the triaging of patients in Emergency Department medicine, hospital acquired infections, new sepsis diagnostic tests and the prevalence of multi drug resistant organisms in a multi-site healthcare network.

We carry out research worldwide supported by academic and clinical experts, and leading academic research centers, in all major medical indication areas. As a result, over the years we have assembled a worldwide database of physicians, laboratory experts, healthcare executives, and operational managers from healthcare networks, academic research institutions, reference laboratories and physician groups. Our research network now covers 47 countries, close to 14,000 institutions and over 38,000 individuals.

We help companies make better decisions because we deliver unique insights on the core business activities that drive growth and profitability. We are uniquely positioned to assist our clients in answering questions fundamental to their business, such as:

- **What is the relevant business environment and how is it changing?**
- **What is the optimal launch strategy and price point to optimize adoption?**
- **What specific actions are required to drive each product to reach its market potential?**

For More Information Please Contact:

Mark Hughes
Vice President
Enterprise Analysis Corporation
203-348-7001
mhughes@eacorp.com