
18-22 Kasım 2015
21.11.2015
12:36:54
JESSICA
SCHILDE
3.Ulusal
Klinik Mikrobiyoloji
Kongresi-2015

# IRIDICA -
## A NEW KIND OF CERTAINTY

**Klimud 2015 / Belek - Antalya**

***Dr. Jessica Schilde***
*Molecular Application Specialist, EMEA*

CHOOSE TRANSFORMATION

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# IRIDICA – A new kind of certainty

## Complete SOLUTION

- An end-to-end solution from specimen to answer
- Sample ID tracking throughout the process
- Automated, simple results reporting

## Comprehensive COVERAGE

- Unprecedented Coverage (bacteria, fungi, and viruses)
- 1,000 pathogens

## Short TURN AROUND TIME

< 6 HOUR Time to First Result

## Direct SAMPLES, different SAMPLE TYPES

- Direct Sample Testing, culture not required.
- Whole blood; Sterile fluids and tissues; BAL, ETA; Plasma

## Reliable IDENTIFICATION

- Identifies one or more pathogens in poly-microbial infections
- Not affected by antimicrobial pre-treatment



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# THE IRIDICA TECHNOLOGY



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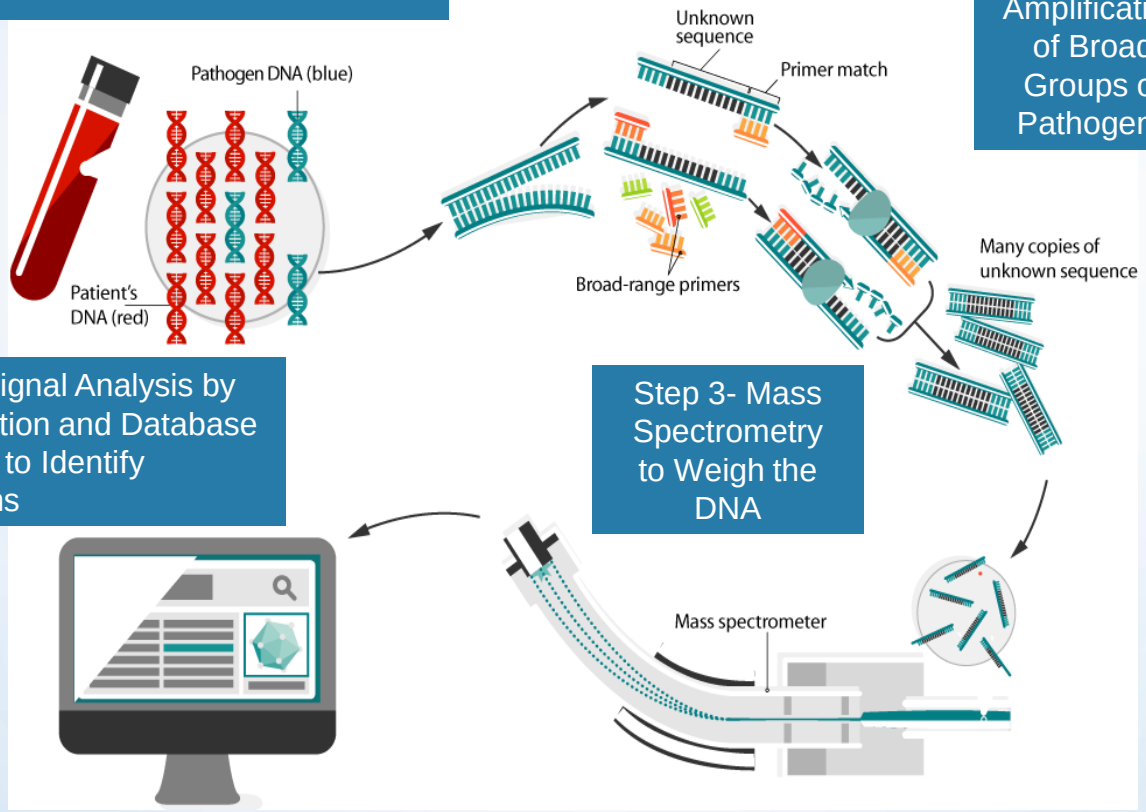
# PCR/ESI-MS Technology

- The IRIDICA technology combines two Nobel-prize winning technologies: PCR and ESI/MS

Step 1- Nucleic Acid Extraction from Direct Specimens: Blood, BAL, ETA, Tissues

Step 2- Unique Primer Design for Amplification of Broad Groups of Pathogens




Step 3- Mass Spectrometry to Weigh the DNA

Step 4- Signal Analysis by Triangulation and Database Matching to Identify Pathogens



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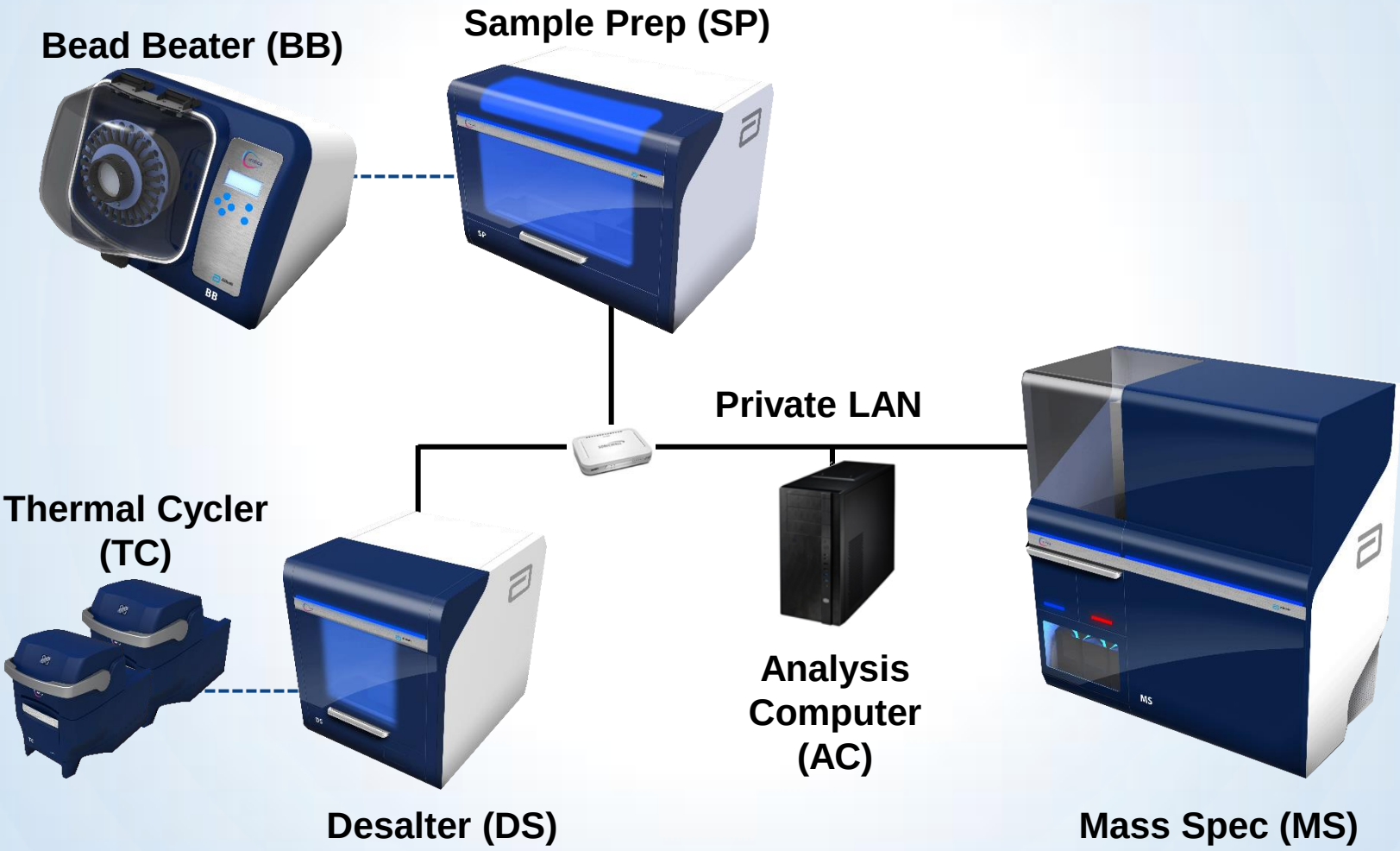
# The IRIDICA Instruments



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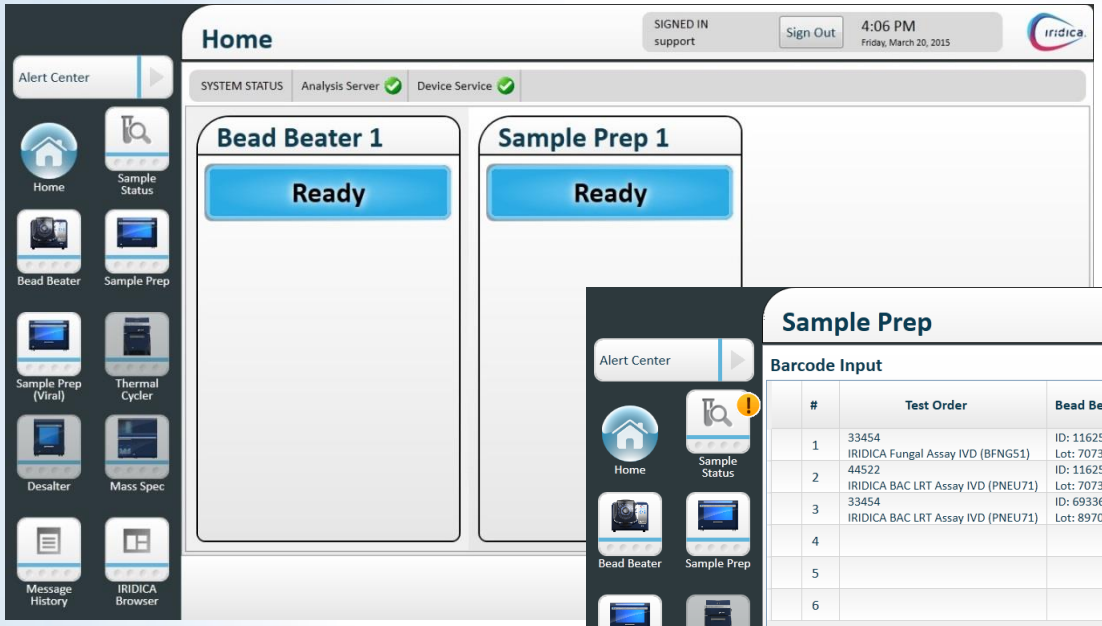
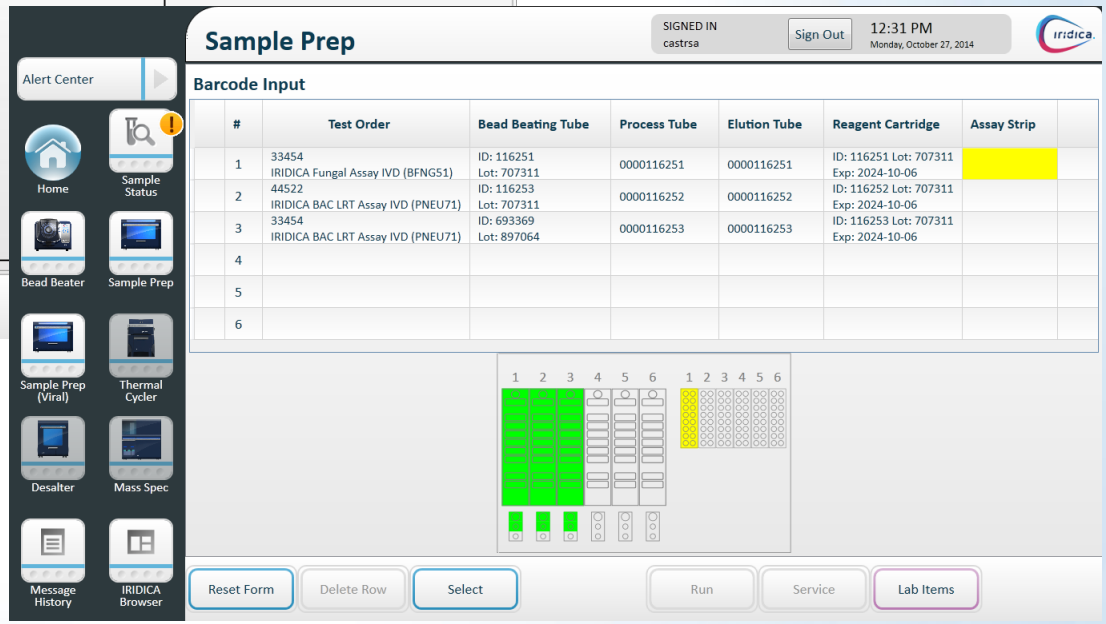
# IRIDICA Software

## Workstation Home Screen




## Sample Prep Loading Screen



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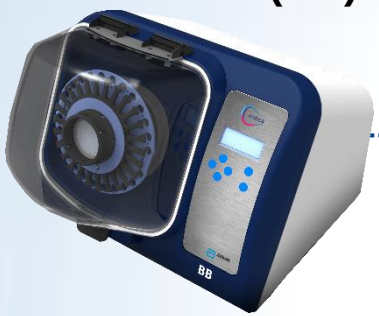
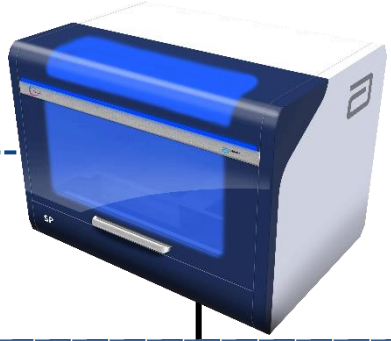
# The IRIDICA Instruments

## Pre-Amplification

Bead Beater (BB)



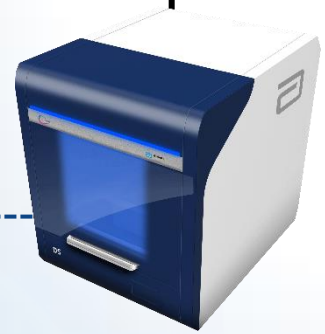
Sample Prep (SP)



## Post-Amplification

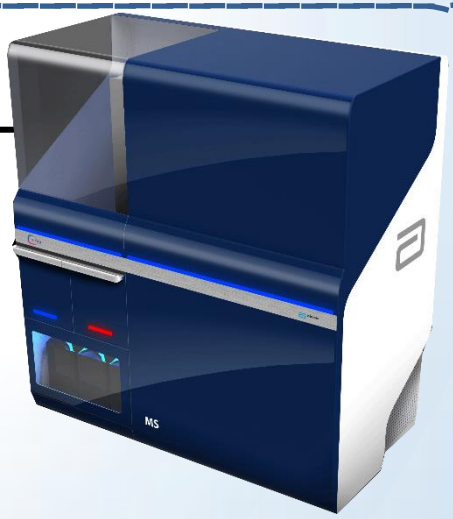
Private LAN

Thermal Cycler (TC)



Desalter (DS)

Analysis Computer (AC)



Mass Spec (MS)



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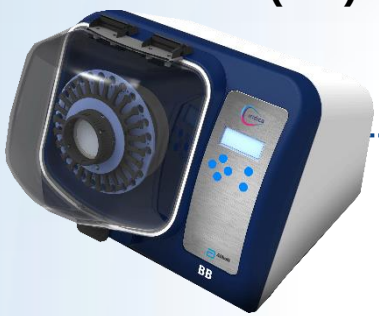
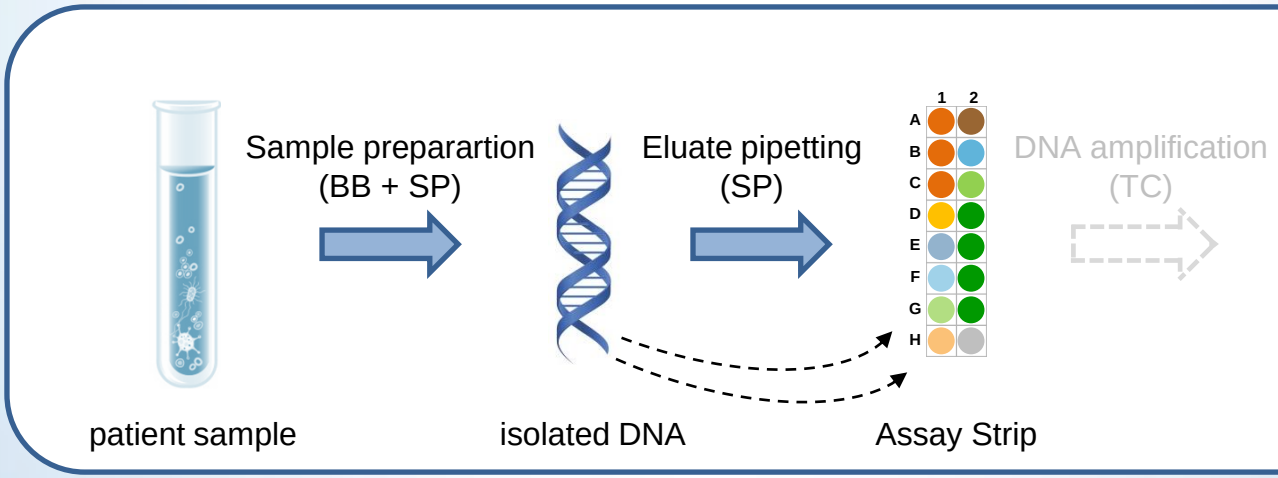
# Pre-Amplification Workflow
## *Nucleic Acid Extraction and Assay Strip Setup*

### Pre-Amplification

**Bead Beater (BB)**




**Sample Prep (SP)**

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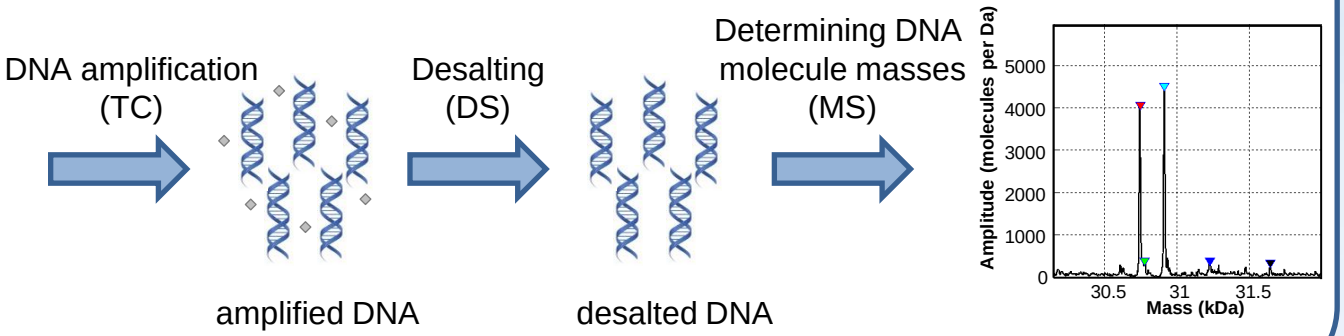
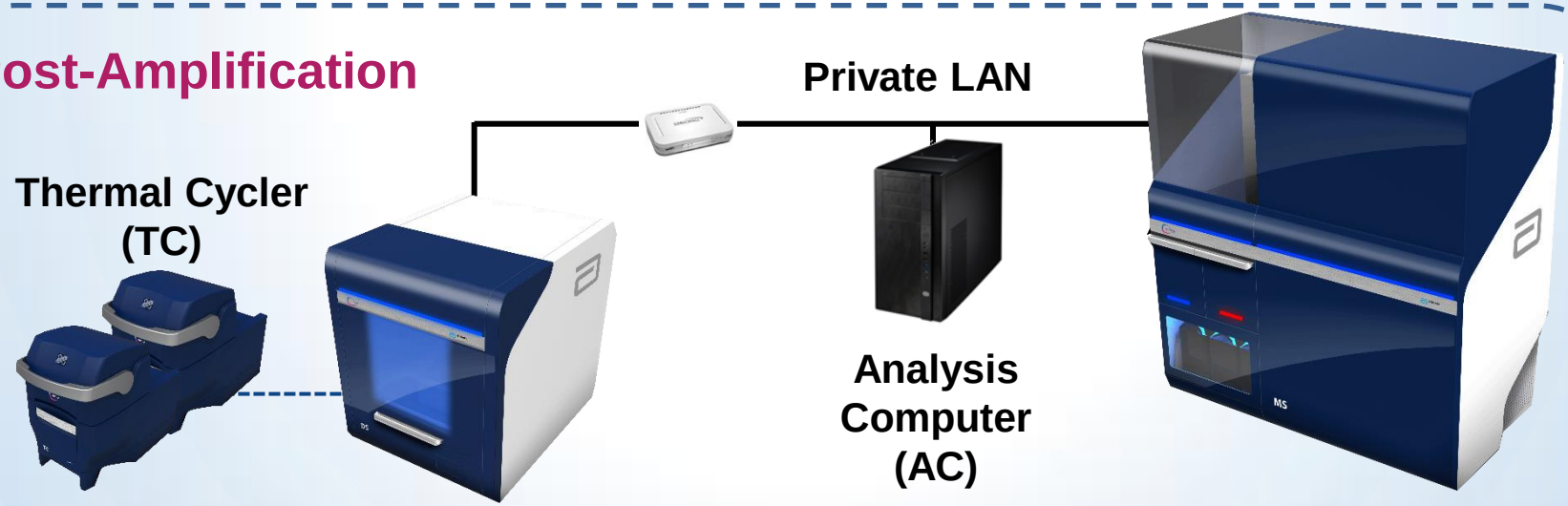
# Post-Amplification Workflow
## *Amplification, Desalting and Analysis*




## Post-Amplification



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# Organism Identification

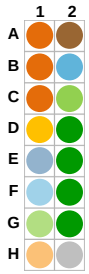
**Sample preparartion (BB + SP)**

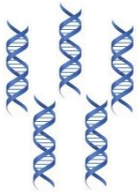
**PCR (TC) Desalting (DS)**

**Determining DNA masses (MS)**

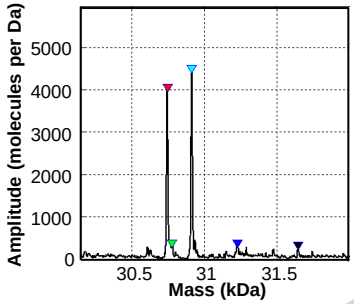
sample

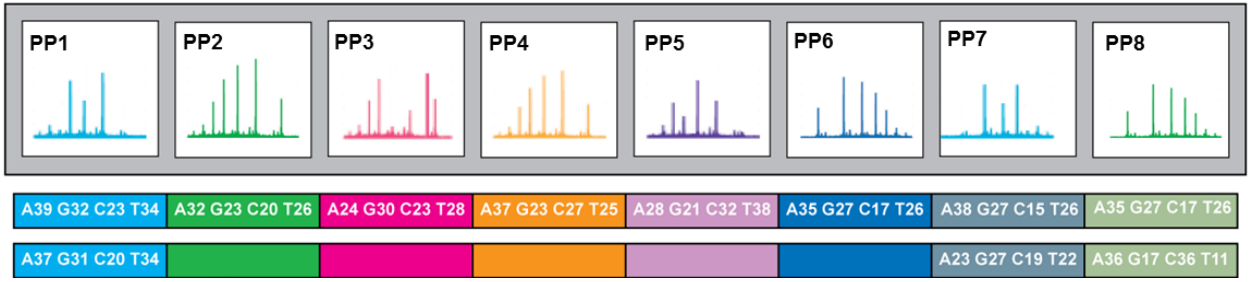
Isolated DNA



amplified & desalted DNA

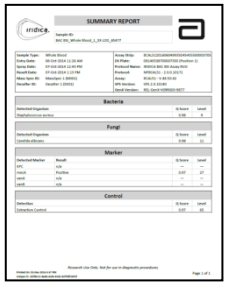



comparison of calculated base compositions to a database

Organism identified

**Detection A**
**Detection B**





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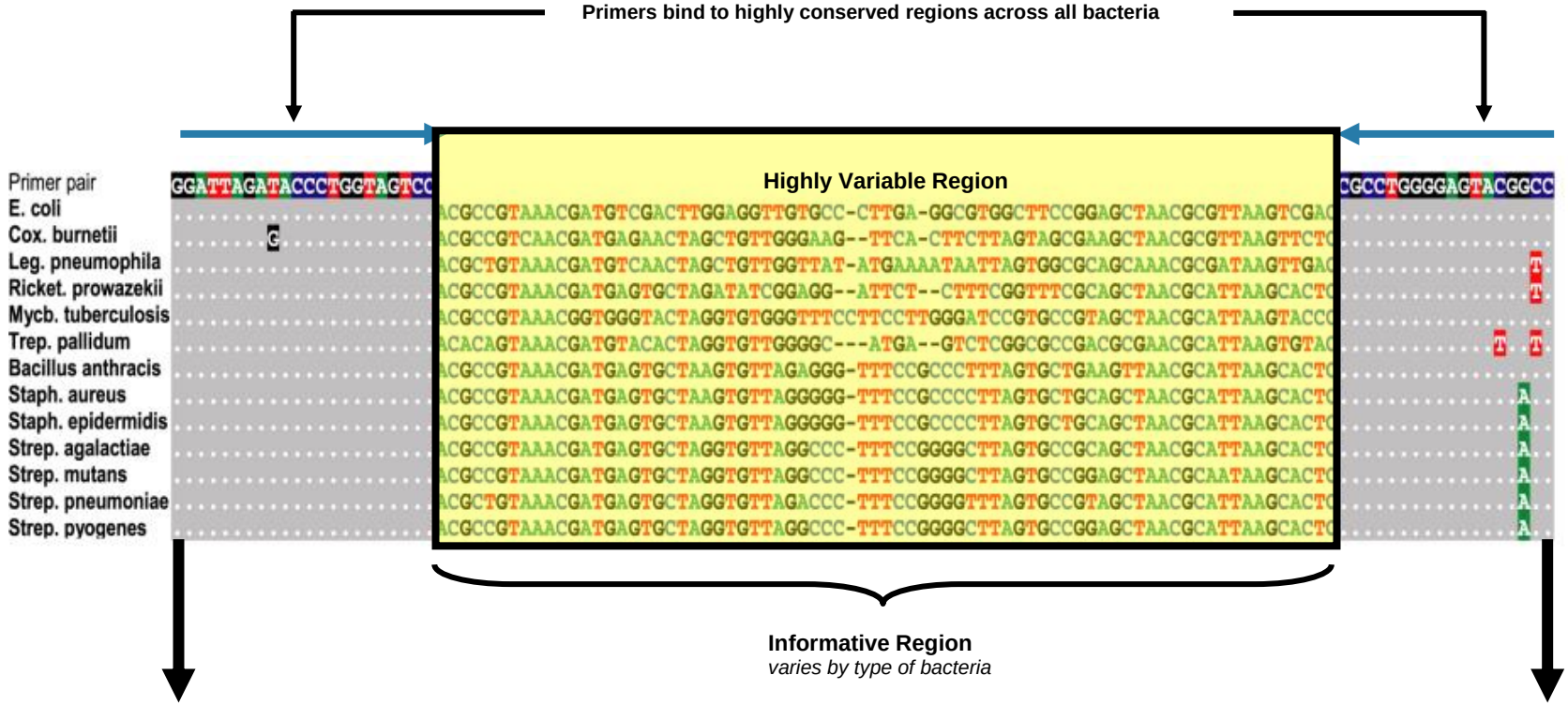
# Broad Amplification

Primers are designed in a way that they span two universally conserved regions not too far apart from each other, but where the nucleotides in between the conserved regions are variable and differ with each unique species.



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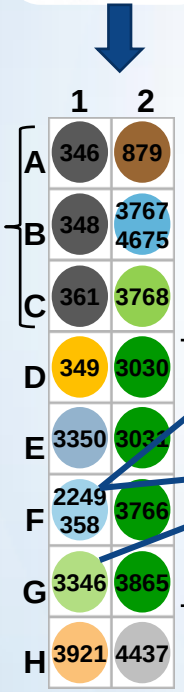
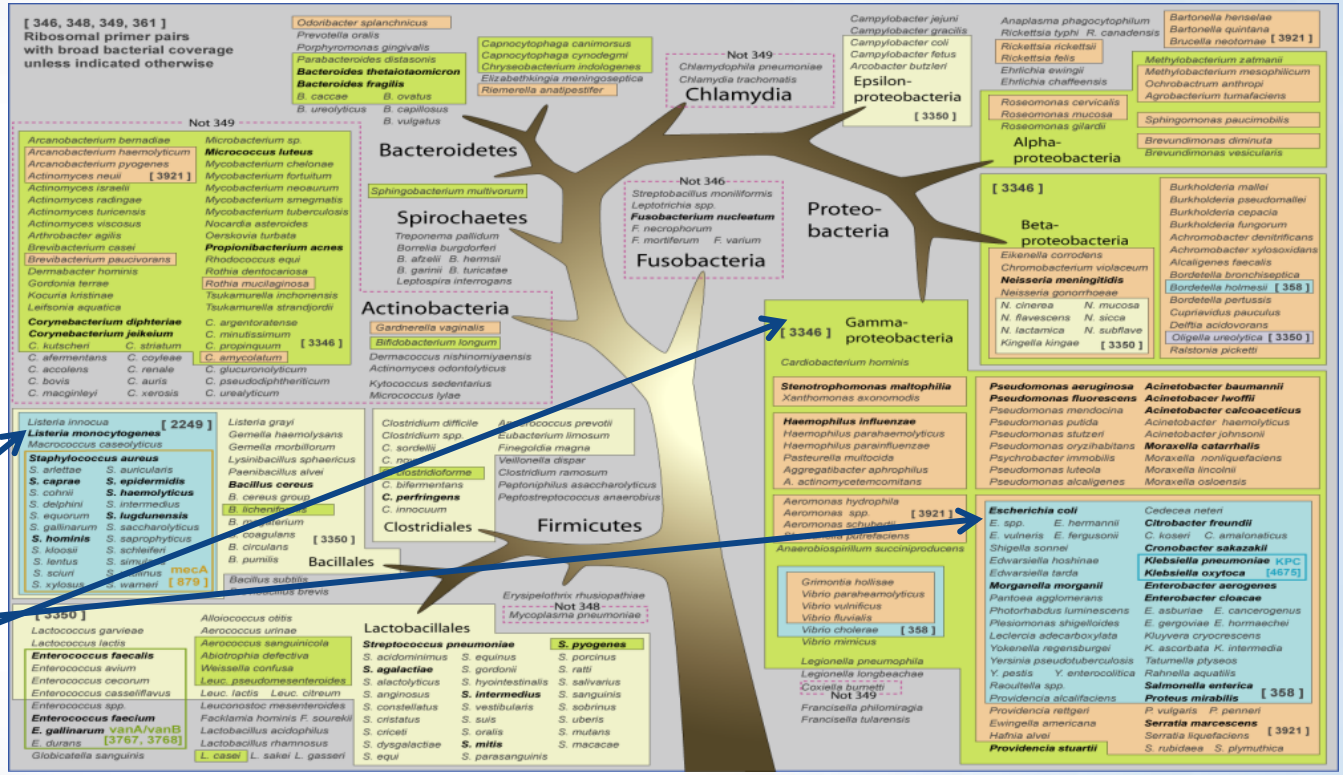
# Broad Amplification



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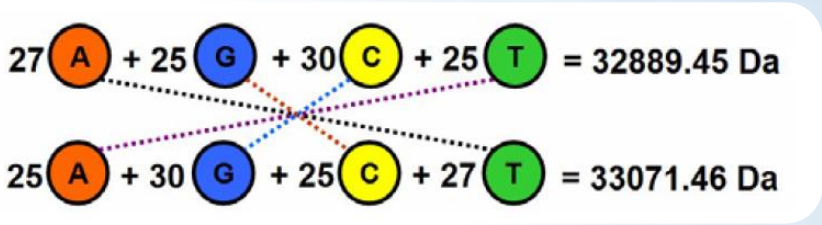
# Mass Spectrometry of PCR Amplicons, Signal Processing and Organism Identification by Triangulation

- Incoming TOF Mass Spectrum
- Calibrate Spectrum
- Determine Masses
- Associate Basecounts with Masses
- Construct Basecount Paths for Organism Hypotheses
- Quantify matching organisms
- Measure Identification Confidences




Triangulation Across Multiple Primers

| Mass | Base Comp. | Quantity |
|---|---|---|
| 30831.72 | A27G30C21T21 | 40341 |
| 36378.33 | A30G29C30T29 | 36030 |
| - | - | No detection |
| 33427.45 | A29G30C25T24 | 40541 |
| - | - | No detection |
| 31271.05 | A26G30C25T20 | 34377 |
| 24373.61 | A16G23C21T19 | 8548 |
| 38952.31 | A43G28C19T35 | 6305 |

Triangulation

***S. aureus*** 6/6 primers

Quantity: 11558

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# SUMMARY REPORT

**Sample ID:** test_4neg

| | | | |
|---|---|---|---|
| **Sample Type:** | Negative Control | **Assay Strip:** | BCAL51201606179935D45541200001625 |
| **Entry Date:** | 23-Oct-2014 8:29 AM | **DS Plate:** | 01351119900001192 (Position 2) |
| **Spray Date:** | 23-Oct-2014 5:48 PM | **Protocol Name:** | IRIDICA BAC BSI Assay IVD |
| **Result Date:** | 23-Oct-2014 5:57 PM | **Protocol:** | NPBCAL51 - 2.0.0.10349 |
| **Mass Spec ID:** | MassSpec 1 (MS01) | **Assay:** | BCAL51 - V.48.50.42 |
| **Desalter ID:** | Desalter 1 (DS01) | **SPS Version:** | SPS.2.0.10354 |
| | | **GenX Version:** | REL-GenX-V09R003-10213 |

IRIDICA Run Detail information

## Flags

WARNING: Negative Control sample has detections.

Assay Flags or Alerts

## Bacteria

| Detected Organism | Q Score | Level |
|---|---|---|
| Staphylococcus aureus | 0.96 | 2 |

## Fungi

| Detected Organism | Q Score | Level |
|---|---|---|
| Not Detected | – | – |

Bacteria and Fungi Detection sections

## Marker

| Detected Marker | Result | Q Score | Level |
|---|---|---|---|
| KPC | n/a | – | – |
| mecA | Not Detected | – | – |
| vanA | n/a | – | – |
| vanB | n/a | – | – |

Drug Resistance Marker section

## Control

| Detection | Q Score | Level |
|---|---|---|
| Extraction Control | 0.97 | 187 |

Extraction Control Detection section



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# Broad Assay Menu and Sample Types

| IRIDICA ASSAY | | Assay Type | Coverage | Selected Diseases/Patient groups |
|---|---|---|---|---|
| BAC BSI | 1 | *Blood stream infection* | 780 Bacteria and *Candida*, 4 Antibiotic Resistance Markers: *mecA*, *vanA*, *vanB* and *kpc* | Sepsis |
| BAC SFT | 2 | *Sterile fluids and tissues* | | Joint prosthetics infection |
| BAC LRT | 3 | *Lower respiratory tract* | Identical coverage with semi-quantitative threshold | Pneumonia, IC patients |
| Fungal | 4 | *Fungal* | > 200 fungi and yeast | Pneumonia, IC Patients |
| Viral IC | 5 | *Viral-Immunocompromised* | 13 viral reporting groups covering > 130 viral species | IC Patients |



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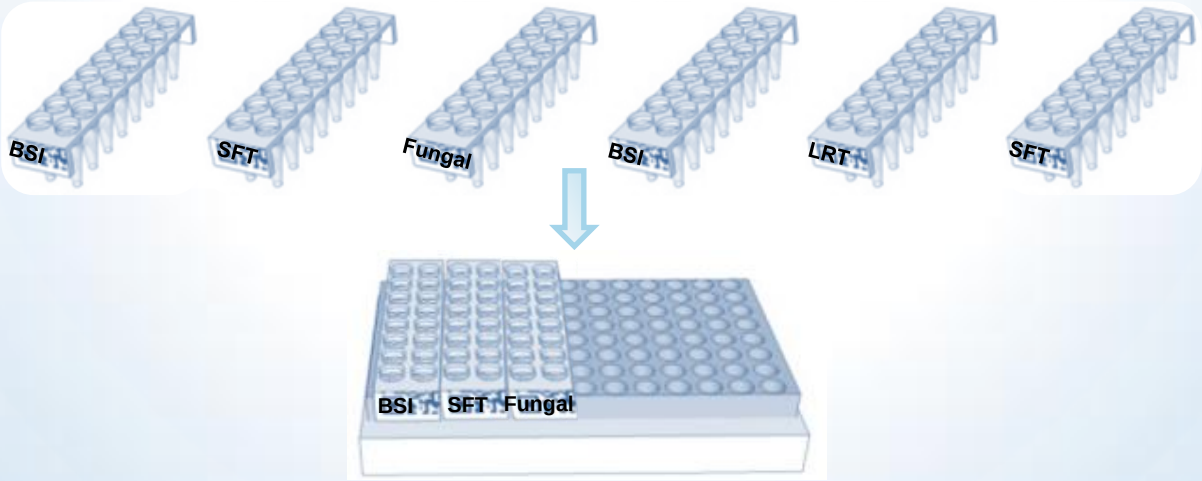
# Parallel processing of different Assays & Samples

EDTA whole blood
Sterile fluid
Sterile tissues
BAL
ETA

Bacteria
Fungi
Antibiotic Resistance
?

Identical DNA Extraction Kit & Procedure



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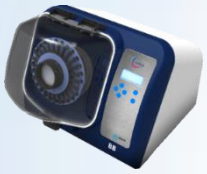
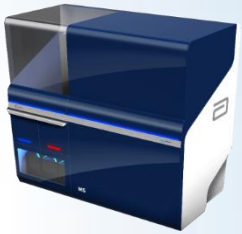
# IRIDICA **Hands-on & Walk-away Times**

| Bead Beater (BB) | Sample Prep (SP) | Thermal Cycler (TC) | Desalter (DS) | Mass Spectrometer (MS) |
|---|---|---|---|---|
|  |  |  |  |  |

## Hands on time (min):

| 15 | 10 | 1 | 5 | 1 |
|---|---|---|---|---|

## Walk away time (min):

| 5 | 110 | 140 – 200 | 35 | 30* |
|---|---|---|---|---|

*Hands on time and walk away time based on in-house data // * To first sample result*



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# STUDIES & PUBLICATIONS



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# The RADICAL Study

## Rapid Diagnosis of Infection in the Critically Ill, a Multicenter Study of Molecular Detection in Bloodstream Infections, Pneumonia, and Sterile Site Infections*

Jean-Louis Vincent, MD, PhD, FCCM[1]; David Brealey, MD[2]; Nicolas Libert, MD[3]; Nour Elhouda Abidi, MD[4]; Michael O'Dwyer, MD[5]; Kai Zacharowski, MD[6]; Malgorzata Mikaszewska-Sokolewicz, MD[7]; Jacques Schrenzel, MD[8]; François Simon, MD[9]; Mark Wilks, PhD[5]; Marcus Picard-Maureau, PhD[10]; Donald B. Chalfin, MD, MPH[11]; David J. Ecker, PhD[11]; Rangarajan Sampath, PhD[11]; Mervyn Singer, MD[2]; the Rapid Diagnosis of Infections in the Critically Ill Team

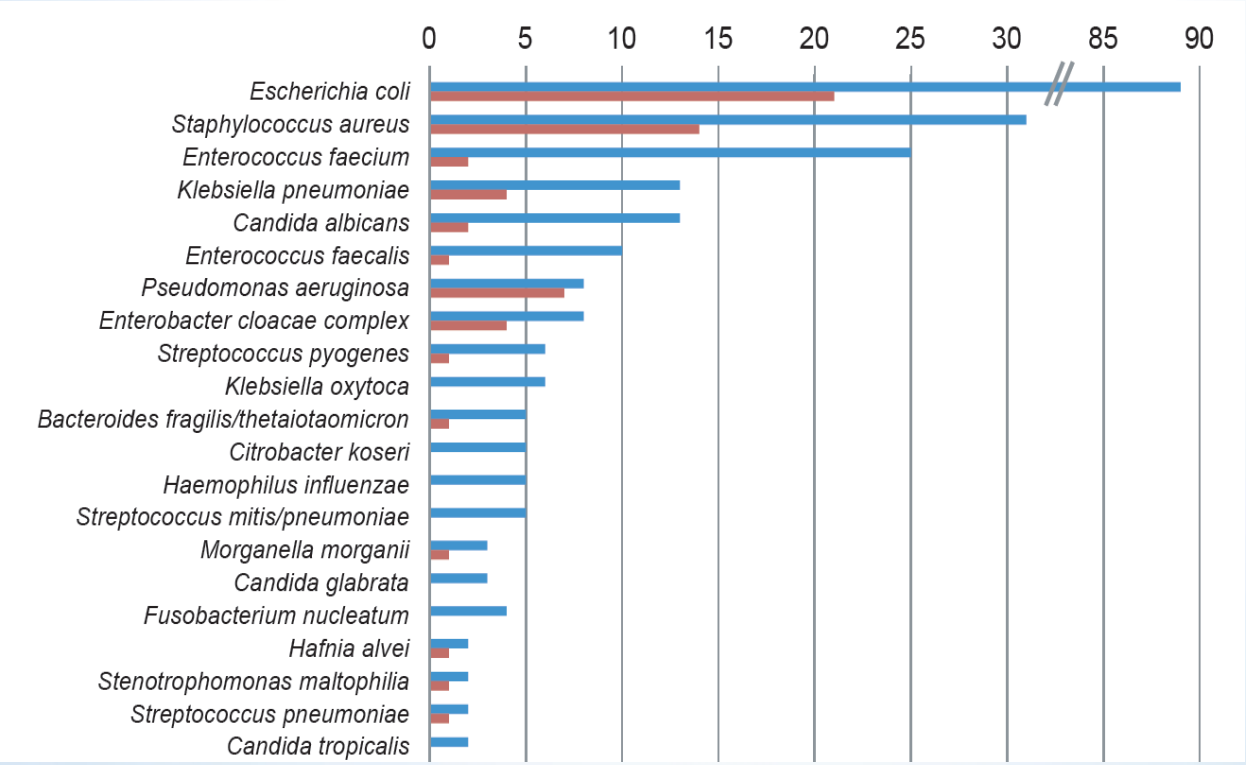
*Critical Care Medicine, 2015 Nov;43(11):2283-91*

- A Multicenter Observational Trial to Evaluate the Potential Clinical Impact of IRIDICA
- Nine ICUs in six European countries as study sites
- Analysis of 616 bloodstream infection,185 pneumonia and 110 sterile fluid and tissue specimens from 529 patients

# The RADICAL Study Key Findings

**Performance against culture in RADICAL:**

- **Sensitivity: >81%**
- **NPV: 97% for blood stream infections**
- **3X greater recovery of pathogens**



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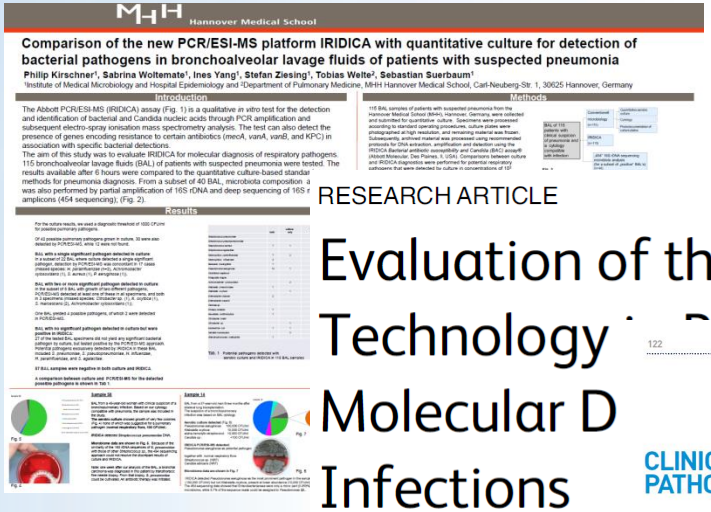
# IRIDICA **Early Assessment Program**



Hannover Medical School

**Comparison of the new PCR/ESI-MS platform IRIDICA with quantitative culture for detection of bacterial pathogens in bronchoalveolar lavage fluids of patients with suspected pneumonia**

Philip Kirschner[1], Sabrina Woltemate[1], Ines Yang[1], Stefan Ziesing[1], Tobias Welte[2], Sebastian Suerbaum[1]

[1]Institute of Medical Microbiology and Hospital Epidemiology and [2]Department of Pulmonary Medicine, MHH Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

Introduction

Methods

Results

RESEARCH ARTICLE

**Evaluation of the Broad-Range PCR/ESI-MS Technology in Blood Cultures for the Molecular D Infections**

Elena Jordana-Lluch[1,2,5], Clara Marcó[1], Mª Jesús [illegible], Vicente Ausina[1,2,5]

122 POINT-OF-VIEW

**CLINICAL BENEFITS OF RAPID PATHOGEN TESTING WITH PCR/ESI-MS**

**Dr. Mark Wilks**, Clinical Scientist, Microbiology at Barts Health NHS Trust in London, UK, talks about their experiences of using PCR/ESI-MS technology over a period of 18 months. During its use for the IMJOIN study, the department also ran clinical samples of interest through the technology.

**How does this technology differ to conventional testing and what are its advantages?**

There are a number of ways in which it differs from conventional microbiology testing. First is the speed of testing. We are used to a kind of 'gardening' approach, where nothing much happens for a minimum of 18 hours or perhaps 2 or 3, whereas with PCR/ESI-MS technology results are available in 6 hours. Another difference is that a lot of bacteria and especially fungi are very difficult to grow and are very slow growing. So with PCR/ESI-MS technology we are getting a lot more positives coming through. With this technology you do not need to try and think of the name of an organism and try to grow it. You rely on the fact that this technology has a very broad coverage and therefore does the thinking for you. You just look for any infectious agent.

**Which patient groups could potentially benefit from the PCR/ESI-MS technology?**

There are a number of distinct clinical groups for which this technology promises to be quite rewarding, including patients with severe sepsis, pneumonia and compromised immune systems. Patients can be immunocompromised because they have recently had a transplant, or they could be haematology oncology or HIV patients. All the immunocompromised groups tend to be infected with unusual bacteria and fungi, which you might not normally look for. In addition ordinary bacteria, which do not harm immunocompetent people, can have serious consequences in this group.

**How would you recommend using this technology to rule in or rule out infections?**

At the moment it is too early to give clear guidance. Obviously if you put the sample through and you get a positive result then it's up to you to decide whether to act on it or not, as with any other test. That is relatively easy compared to ruling out infections where you are relying on the high negative predictive value of the technology to rule out infections. This requires a lot of confidence and experience for people to act on that result and therefore to stop treating and maybe stop looking for further agents.

**Why is the high negative predictive value so important in ruling out infections in patients?**

The main hope is that we'll have enough confidence in the results to rule out infection. For example, a lot of patients in ICU, who were thought to be septic, actually don't have any infection at all. They might have SIRS, but that could be nothing to do with infection - it could be due to surgery, trauma or another reason. But obviously the possibility of infection has to be considered and treatment may well be started. And there may be no underlying infection at all. What we hope is that our experience so far with ruling out infection will be maintained, and that we will have increasing confidence to act on the results and not to narrow antibiotic treatment or stop antibiotic treatment. In patient groups such as haematology oncology patients there is a huge amount of prophylactic anti-fungal treatment, despite the fact that clinicians don't really have any evidence of the patient having a fungal infection. However, the consequences of not treating an invasive fungal infection are so serious that they dare not take the risk. This has implications for costs as well, if they can rule out having to treat these patients. Barts and London NHS Trust, for example, spends up to two million pounds per year on antifungal treatment, much of which is almost certainly unnecessary.

Another patient group where this high negative predictive value is important is preterm babies, who are admitted to neonatal intensive care units with possible sepsis. Often they are given five days or more antibiotic treatment. The consequences of unnecessary antibiotic treatment are extremely serious. It is not just the question of unnecessary treatments and encouraging antibiotic resistance. It can double their chances of getting necrotising enterocolitis and late-onset sepsis and death. ■

DISCLOSURE:
'Point-of-View' articles are part of the ICU Management Corporate Engagement Programme

**Direct detection of *Mycobacterium tuberculosis***

1 year old boy with possible septic arthritis in one elbow, but all testing for bacteria and viruses was negative. We tested a specimen of his synovial fluid with PCR/ESI-MS technology, and to our complete astonishment we detected Mycobacterium tuberculosis. To make matters more confusing, in the same group of three or four specimens Mycobacterium tuberculosis was also detected directly from blood in a 67-year-old male patient in ICU. I was frankly skeptical about the results, thinking that at least one was a contaminant and maybe both were artifacts of some kind! And we repeated the tests several times after cleaning everything with bleach always with the same result. In fact both cases turned out to be genuine. Although the boy had no family history of TB or travel history, he did have an IL12/Th1b imbalance. There was no question of treating him as the test was not CE marked at the time, but over a month later we grew Mycobacterium tuberculosis from his elbow and typing showed that it was in fact Bacillus Calmette-Guérin (BCG) and treatment was started. The 67-year-old male patient on ICU turned out to be a multi-drug resistant tuberculosis patient, which was not known to the admitting physicians.

16-year-old male builder, PMH of lymphoma. Admitted septic, meningitic (first CT scan brain reported normal), one eye was "bulging" and there were cavities on chest x-ray. Repeat CT Head scan showed possible intracerebral lesions. All conventional microbiology and virology were negative. There was a debate about this being a possible fungal infection or TB meningitis; in fact he was put on quadruple therapy for TB vancomycin, isaxcin and ambisome. PCR/ESI-MS of his BAL detected Candida and several other anaerobic bacteria which are hard to grow. The addition of metronidazole to cover anaerobes led to a rapid improvement and probably saved his life. The patient's poor dentition then fitted in with aspiration pneumonia and anaerobic cerebral abscesses, but without the hint we may never have treated the patient in time.

ICU Management 3 - 2015

123 POINT-OF-VIEW

Thank you!