SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna

ALMA MATER STUDIORUM
A.D. 1088

(we are not curing lab results)
Management of Diagnostic Tests

XX. TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI KONGRESİ

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U.O. MICROBIOLOGIA
Pievesestina

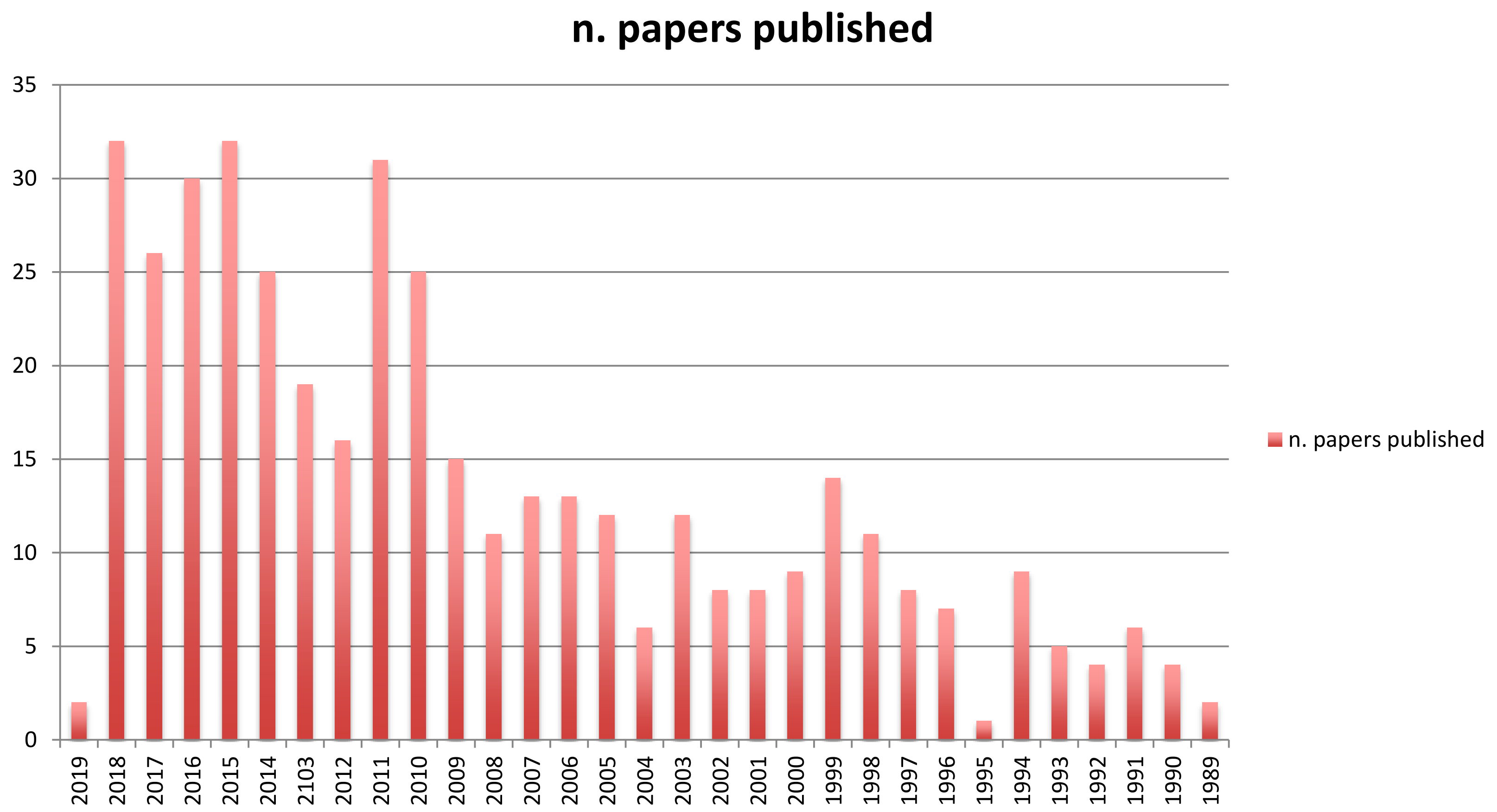
Financial disclosure

- **Speaker's Grants:**
  - GenePOC CANADA
  - TechnoGenetics
  - ADA
  - Synttergy Consults
  - DiaSorin
  - COPAN
  - Arrows Diagnostics
  - Eiken Chemicals Japan
- **Research Grants:**
  - DiaSorin
  - Siemens HealthCare
  - Abbott IRIDICA
  - bioFire
  - Orion Diagnostica
  - VirCell
  - SD Biosensors
  - ADA

Agenda

- A large portfolio of diagnostic tests: do we really need them?
- **If yes** how to choose among the various technologies? Syndromic or not?
- Blood stream Infections (a paradigma)
    - Blood Culture
        - Pheno
        - Molecular
    - Primary whole blood sample

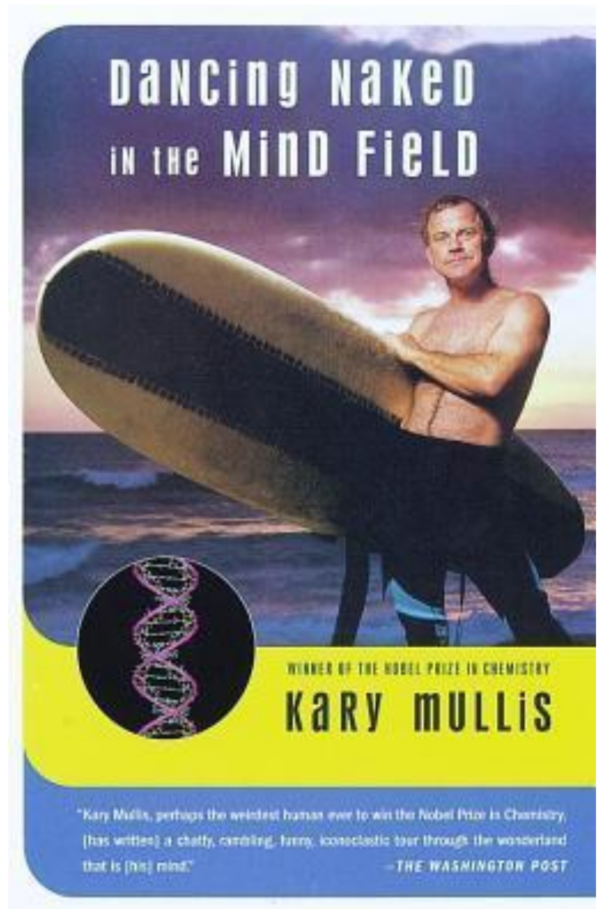
pubmed - fast microbiology diagnosis



What is now available

- Reduced TAT
- Fast Microbiology Techniques
  - Pheno (Fast MALDI-ToF, Accelerate, Q-linea….)
  - Geno (FISH, RT-PCR panels, T2…..)
- Primary specimens (many available for LRTI/URTI/UTI but a few methods presently available for bacteriemia)
- ***DIAGNOSTIC STEWARDSHIP***

Everything started from here



Microbial Detection, Identification, and Drug-Susceptibility Testing

- MOLECULAR PROBES
- PCR
- RT-PCR
- SEQUENCING (SANGER AND/OR NGS)
- ISOTHERMAL AMPLIFICATION
- MALDI ToF

Germ/Disease

One by One

- Anthrax (*Bacillus anthracis*)
- TB (*Mycobacterium tuberculosis*)
- Poliomyelitis (Poliovirus)
- *Syphilis (Treponema pallidum*)
- Rubella (Rubeovirus)
- ....

One by MORE than one

- Meningitis
  - *N.meningitidis*
  - *S.pneumoniae*
  - Enteroviruses
  - TosV
  - ....
- Pneumonia
  - *S.pneumoniae*
  - *M.pneumoniae*
  - *L.pneumophila*
  - Influenza virus
  - ....

Pros/Cons

Classic Microbiology

- Growth is an ISSUE
  - Sample transport & conservation
  - Media
  - Antibiotic therapy
  - TAT (24 hours)
  - Minimal germ load required
- Monimicrobic infections
- AST delivers MIC
- Living (pathogenic) germs

Molecular Microbiology

- Growth IS NOT an ISSUE
  - Inhibition
  - Internal Control
  - NA extraction efficiency
  - Short TAT (minute/hours)
  - Very low LOD
- Multiplexing/Polymicrobic Infections
- Limited pattern of genes
- Portions of DNA/RNA detected (who cares about antibiotics?)
- Microbioma/Virusoma/…omas

A “syndromic” approach

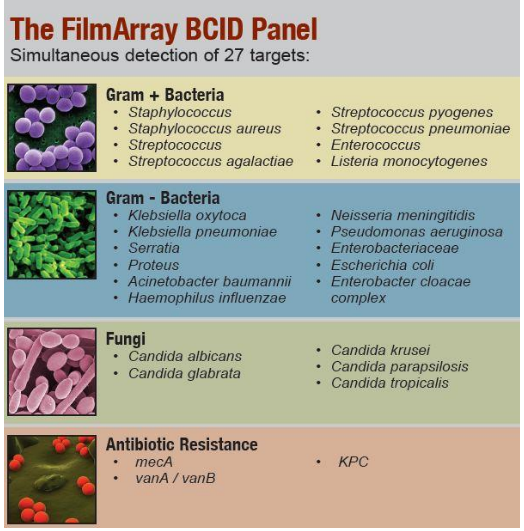
- Classic Microbiology
  - Culture based
  - Phenotypic ID
  - Phenotypic AST
  - Immunocomplex ID
  - Immune response detection
  - **Time is an issue**
  - First come First got

- Molecular Microbiology
  - Specific gene(s) ID
  - Growth is not necessary (***sometime!***)
  - Multiple techniques
  - Very low LOD
  - **Fast and quick**
  - More germs “who is the bad guy”

Open issues...

- Fast Microbiology techniques are labor and cost intensive
- Who are the “right patients”
- Clinical Selection (Ward or clinical scores)
- Legal issues

FilmArray® Blood Culture Identification Panel (BioFire)



GeneXpert Carba-R (Cepheid)

GROUP	PATHOGEN
Gram-positive bacteria	*Staphylococcus aureus*
	Streptococcus pneumoniae
Enterobacteriaceae	*Citrobacter freundii*
	Escherichia coli
	Enterobacter cloacae complex
	Enterobacter aerogenes
	Proteus spp.
	Klebsiella pneumoniae
	Klebsiella oxytoca
	Klebsiella variicola
	Serratia marcescens
	Morganella morganii
Non-fermenting bacteria	*Moraxella catarrhalis*
	Pseudomonas aeruginosa
	Acinetobacter baumannii complex
	Stenotrophomonas maltophilia
	Legionella pneumophila
Others / Fungi	*Pneumocystis jirovecii*
	Haemophilus influenzae
	Mycoplasma pneumoniae
	Chlamydophila pneumoniae

GENE	RESISTANCE AGAINST
ermB	Macrolide/Lincosamide
mecA	Oxacillin
mecC (LGA251)	Oxacillin
tem	Penicillin
shv	Penicillin
ctx-M	3rd generation Cephalosporins
kpc	Carbapenem
imp	Carbapenem
ndm	Carbapenem
oxa-23	Carbapenem
oxa-24/40	Carbapenem
oxa-48	Carbapenem
oxa-58	Carbapenem
vim	Carbapenem
sul1	Sulfonamide
gyrA83	Fluoroquinolone
gyrA87	Fluoroquinolone

Unyvero P55 (Curetis AG)

Syndromic Panel-Based Testing in Clinical Microbiology

Poornima Ramanan,[a] Alexandra L. Bryson,[a] Matthew J. Binnicker,[a] Bobbi S. Pritt,[a,b] Robin Patel[a,b]

TABLE 1 FDA-approved/cleared panel-based molecular assays for detection of select microorganisms and select resistance genes in positive blood culture bottles

Parameter	FilmArray BCID	Verigene: Gram-positive blood culture	Verigene: Gram-negative blood culture
Total no. of targets	27	15	14
Ability to detect pathogen			
Gram-positive bacteria			
Staphylococcus species	✓	✓	
Staphylococcus aureus	✓	✓	
Staphylococcus epidermidis		✓	
Staphylococcus lugdunensis		✓	
Streptococcus species	✓	✓	
Streptococcus agalactiae	✓	✓	
Streptococcus pyogenes	✓	✓	
Streptococcus pneumoniae	✓	✓	
Streptococcus anginosus group		✓	
Enterococcus species	✓		
Enterococcus faecalis		✓	
Enterococcus faecium		✓	
Listeria species		✓	
Listeria monocytogenes	✓		
Gram-negative bacteria			
Klebsiella oxytoca	✓		✓
Klebsiella pneumoniae	✓		✓
Serratia marcescens	✓		
Proteus species	✓		✓
Acinetobacter species			✓
Acinetobacter baumannii	✓		
Haemophilus influenzae	✓		
Neisseria meningitis	✓		
Pseudomonas aeruginosa	✓		✓
Enterobacteriaceae	✓		
Escherichia coli	✓		✓
Enterobacter species			✓
Enterobacter cloacae complex	✓		
Citrobacter species			✓
Yeasts			
Candida albicans	✓		
Candida glabrata	✓		
Candida krusei	✓		
Candida parapsilosis	✓		
Candida tropicalis	✓		
Ability to detect presence of resistance gene			
mecA	✓	✓	
vanA	✓	✓	
vanB	✓	✓	
bla_{KPC}	✓		✓
bla_{NDM}			✓
bla_{OXA}			✓
bla_{VIM}			✓
bla_{IMP}			✓
$bla_{CTX\text{-}M}$			✓
Time to result (h)	~1	~2.5	~2

vittorio sambri_Antalya KLIMIK 2019
march 15

Assessment of Rapid-Blood-Culture-Identification Result Interpretation and Antibiotic Prescribing Practices

Linsey M. Donner,[a] W. Scott Campbell,[b] Elizabeth Lyden,[c]
Trevor C. Van Schooneveld[d]

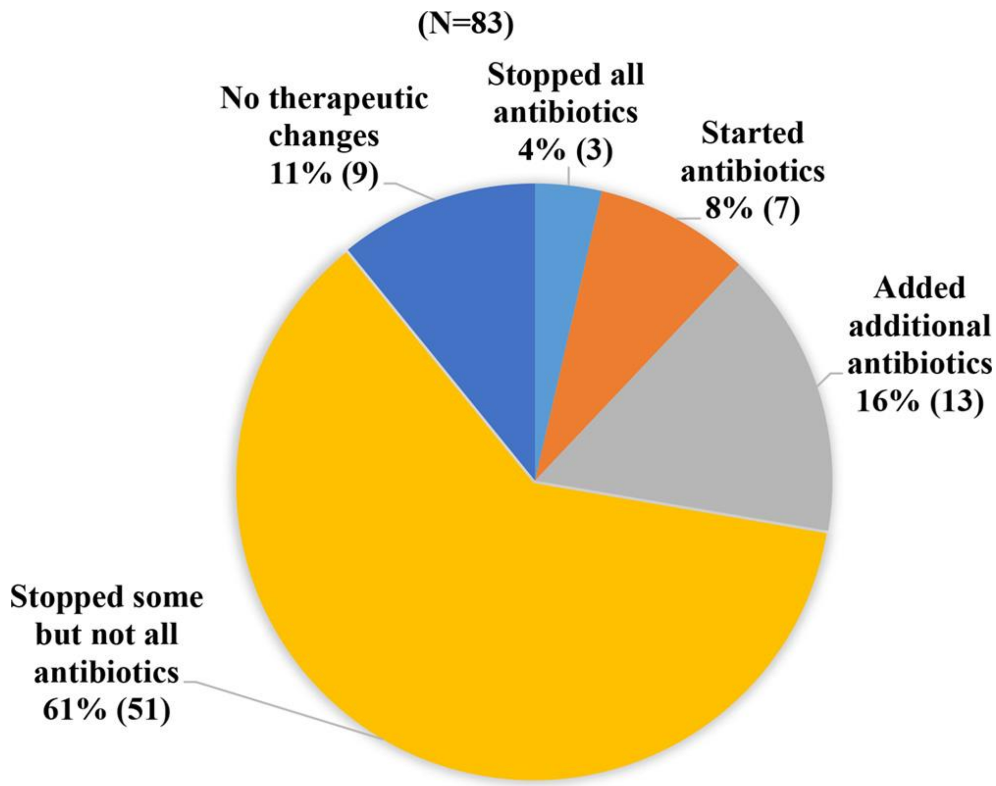
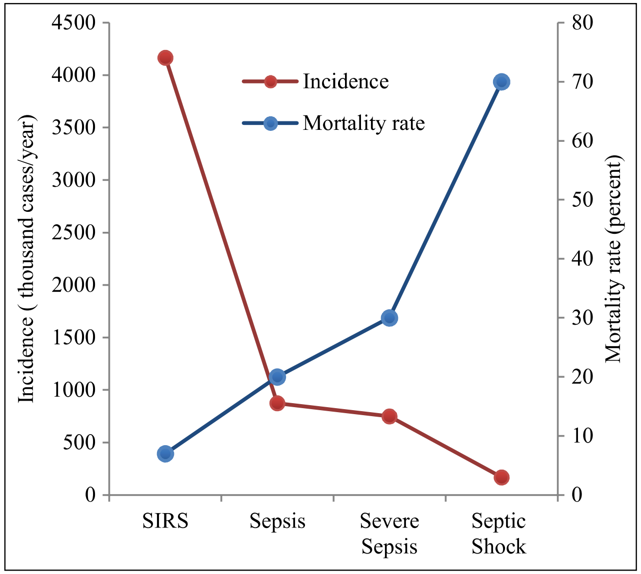


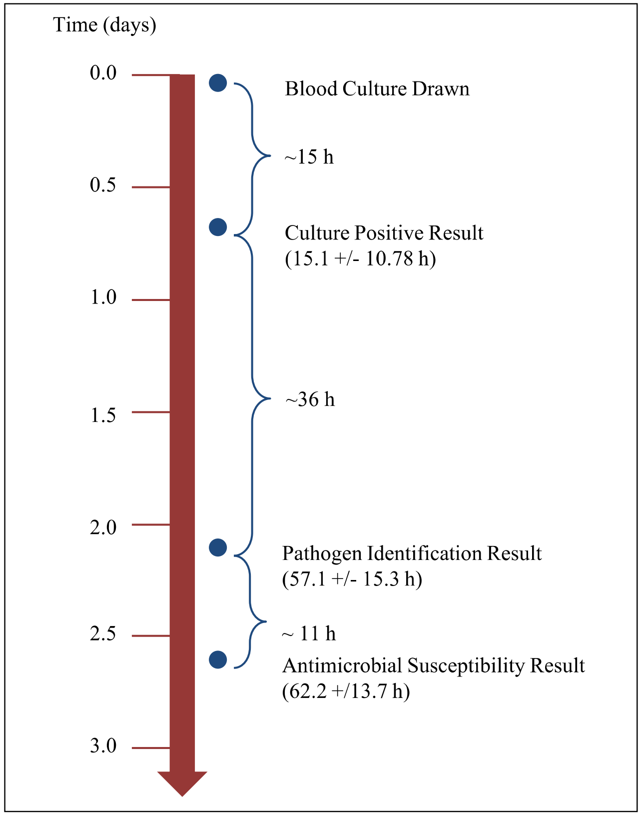
FIG 1 Self-reported changes in antibiotic therapy frequently made based on BCID results.

May 2017 Volume 55 Issue 5 Journal of Clinical Microbiology

Sepsis Pathogen Identification

Katy Chun[I], Chas Syndergaard[I], Carlos Damas[I], Richard Trubey[I], Amruthavani Mukindaraj[I], Shenyu Qian[I], Xin Jin[I], Scott Breslow[I], and Angelika Niemz[I]





Journal of Laboratory Automation 20(5)

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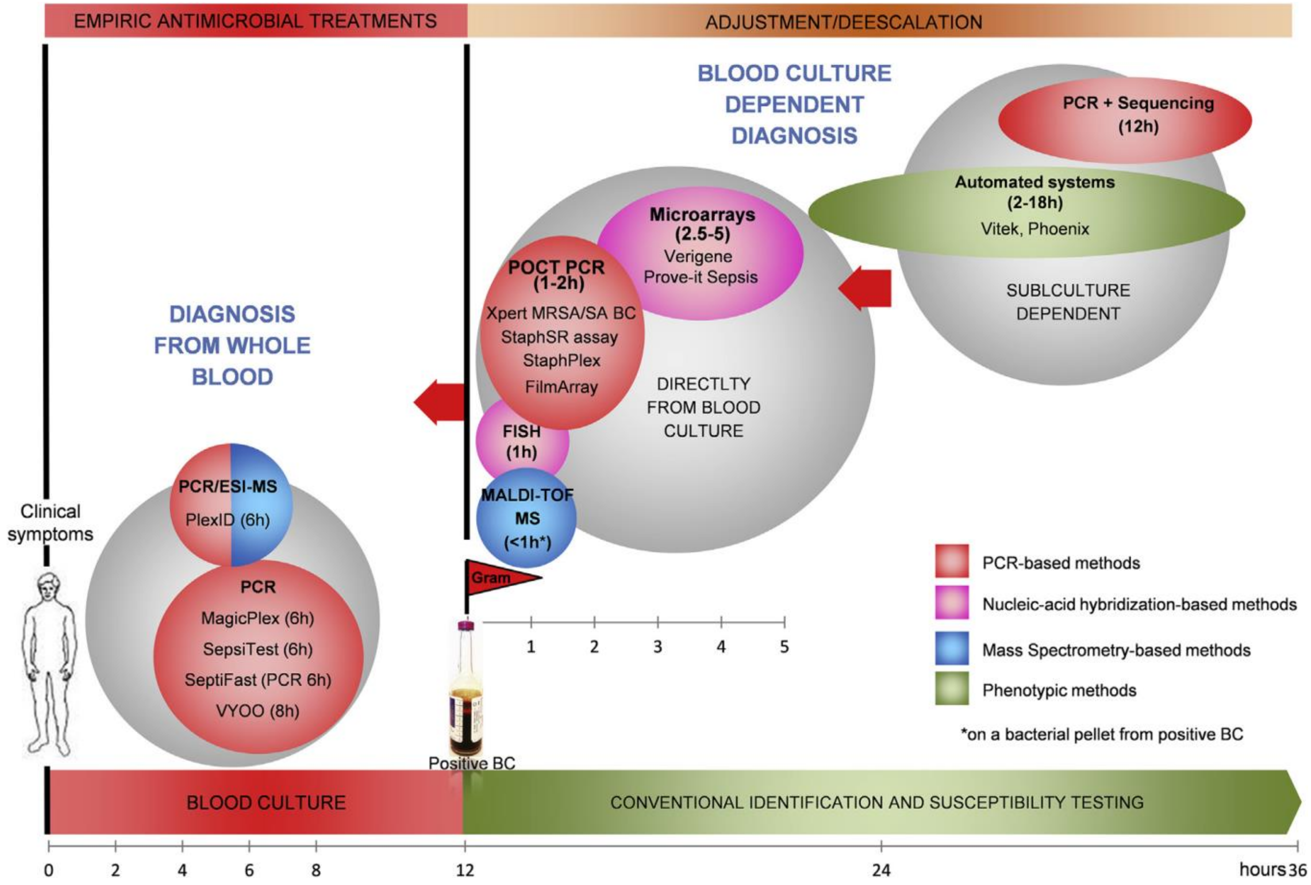


FIG. 2. Nucleic acid methods for the microbial diagnosis of BSI, BC-independent and BC-dependent methods. Nucleic acid–based methods have shortened the time to result BSI diagnosis. In the absence of microbial documentation of the etiologic agent of the BSI, anti-infectious treatments are initiated on the basis of clinical and epidemiologic information. Diagnosis directly from blood samples could shorten the length of empiric treatment.

Opota *et al.* Diagnosis of bacteremia directly from blood

Current concepts in the diagnosis of blood stream infections. Are novel molecular methods useful in clinical practice?

Reetta Huttunen [a,b,*], Jaana Syrjänen [a,b], Risto Vuento [c], Janne Aittoniemi [c]

[a] Department of Internal Medicine, Tampere University Hospital, Box 2000, FI-33521 Tampere, Finland
[b] University of Tampere Medical School, University of Tampere, Tampere, Finland
[c] Fimlab Laboratories, Pirkanmaa Hospital District, Tampere, Finland

International Journal of Infectious Diseases 17 (2013) e934–e938

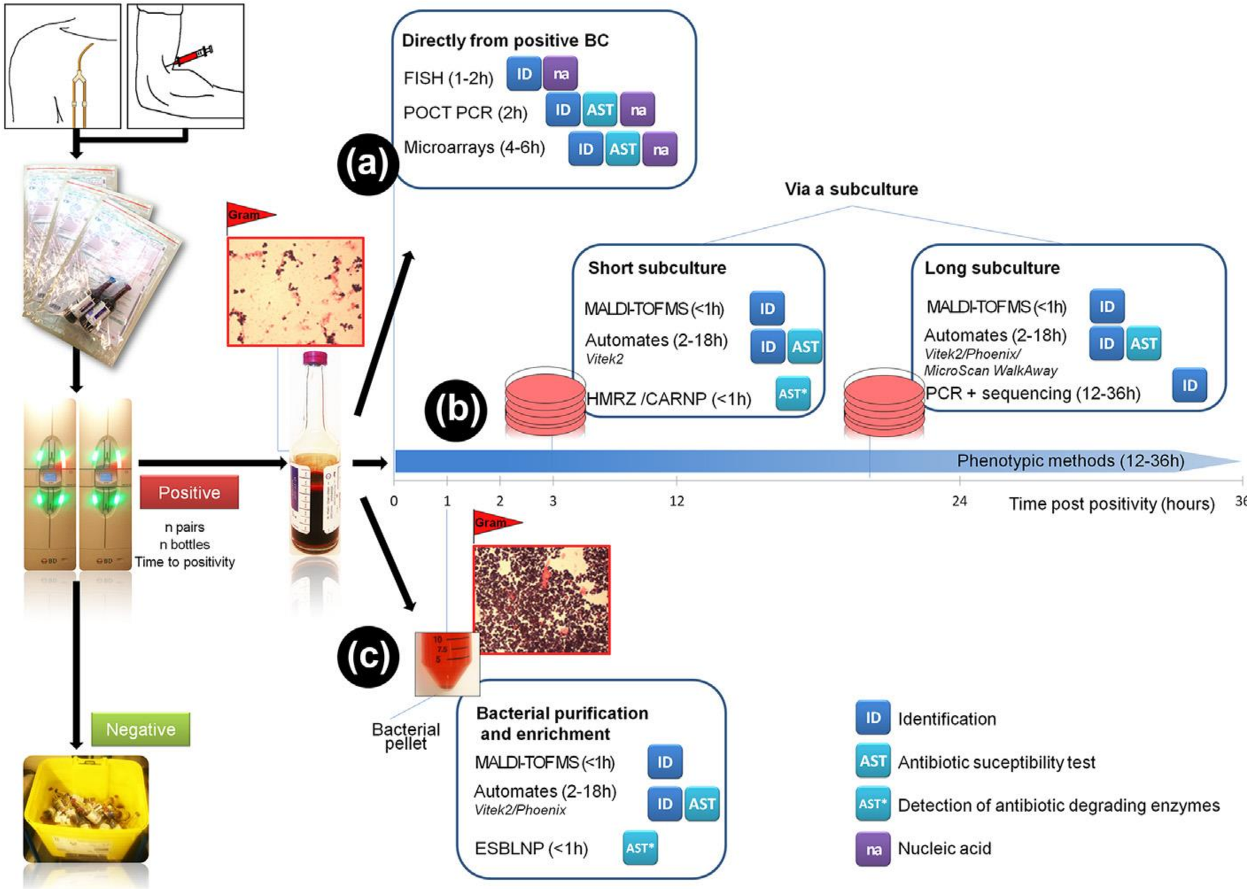
Table 2
Schematic turnaround times of novel molecular methods in the detection of bacteremia

Method	Turnaround time after positive blood culture	Turnaround time after whole blood sample
Culture growth needed		
Hybridization techniques	1.5–3 h	12–24+ (1.5–3 h)
Amplification techniques	1–8 h	12–24+ (1–8 h)
Mass spectrometry methods	4–6 h	12–24+ (4 h)
Directly from blood sample		
Whole blood amplification methods	-	6 h

Blood culture-based diagnosis of bacteraemia: state of the art

O. Opota[1], A. Croxatto[1], G. Prod'hom[1] and G. Greub[1,2]

1) *Institute of Microbiology and* 2) *Infectious Diseases Service, University of Lausanne and University Hospital Centre, Lausanne, Switzerland*



Clin Microbiol Infect 2015; **21:** 313–322

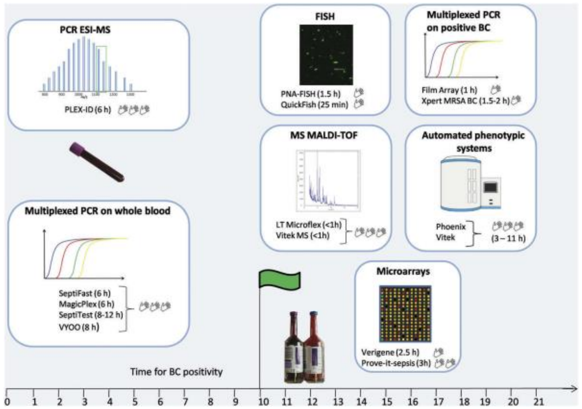
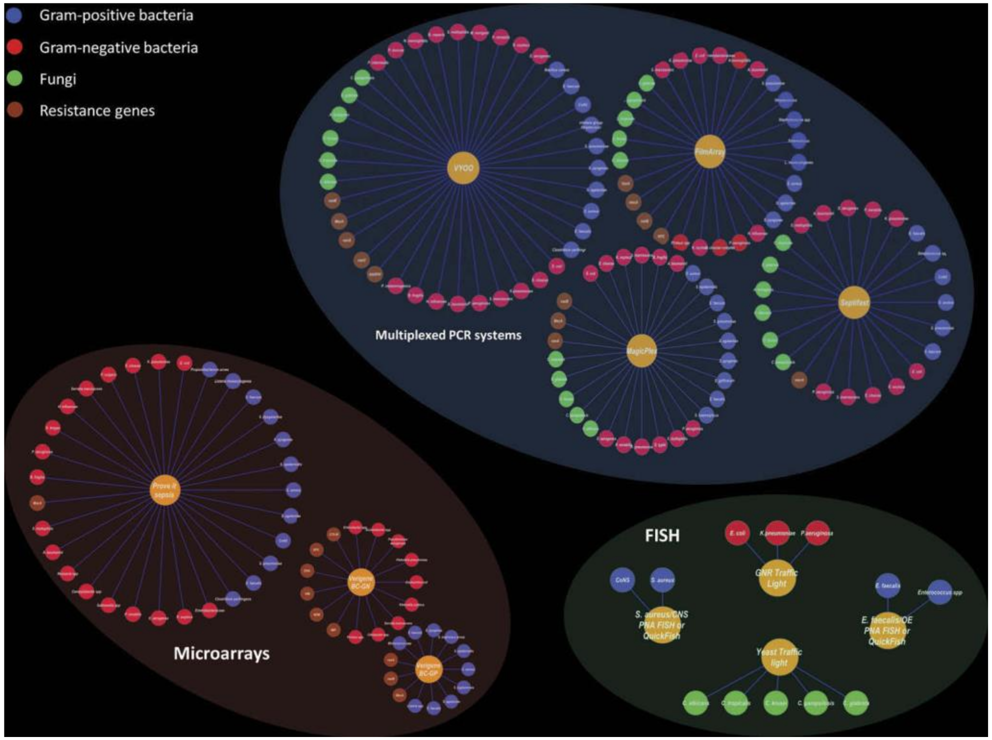


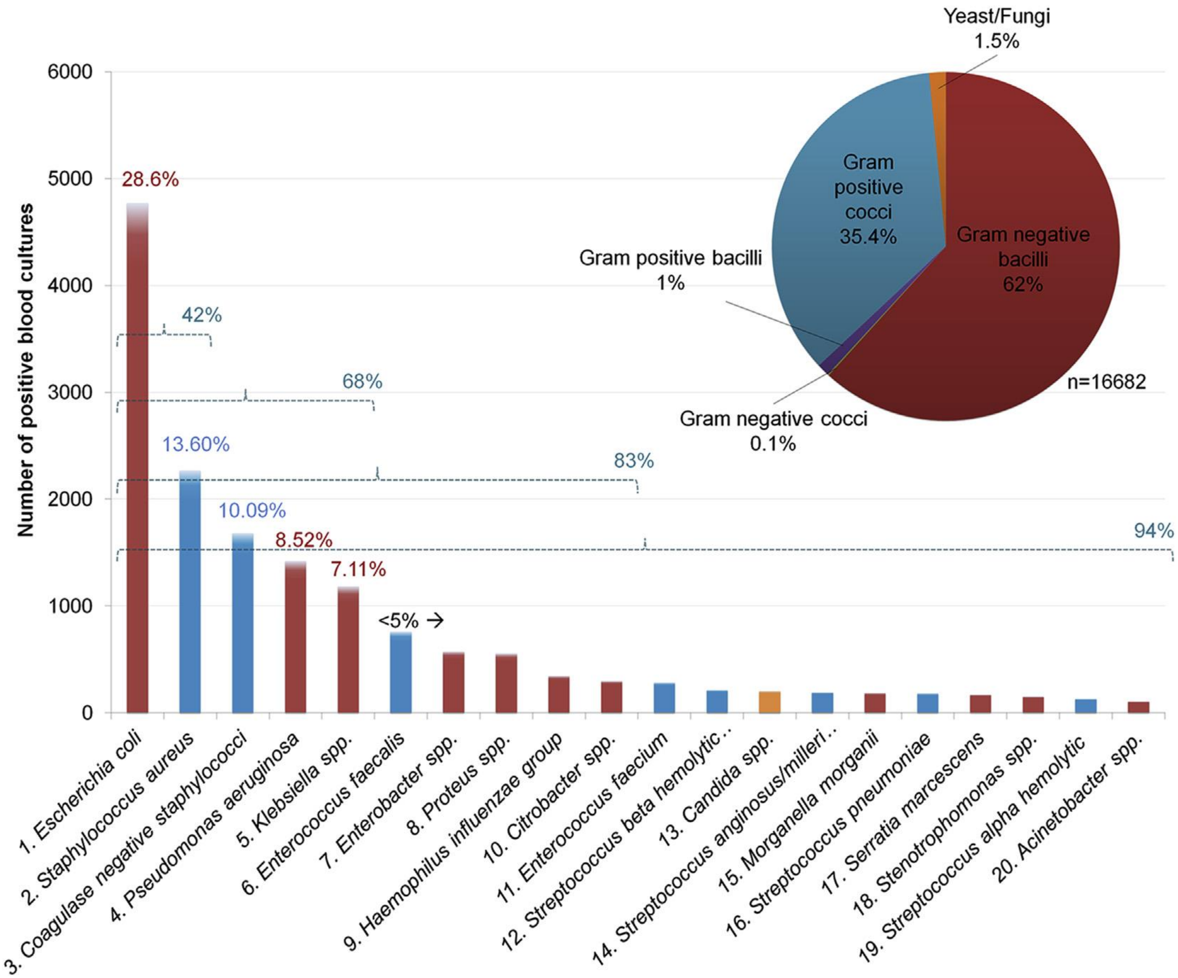
Figure 1. Detection methods for the early diagnosis of bloodstream infections, performed on whole blood or positive blood culture. Number of hands represent the hands-on time (one : <10 minutes; two: 10–30 minutes; three: >30 minutes).

Emerging methodologies for pathogen identification in positive blood culture testing

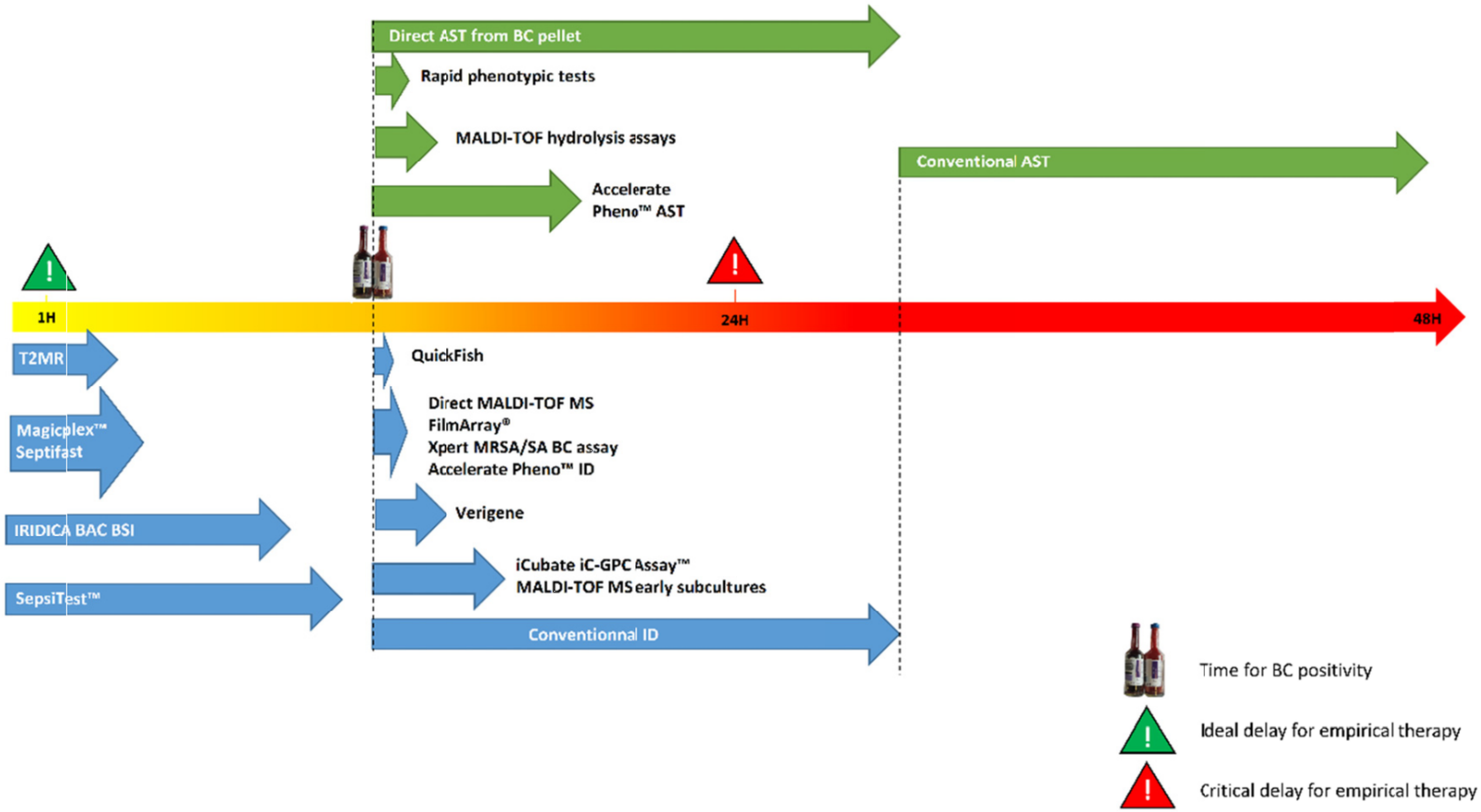
Grégory Dubourg & Didier Raoult



Expert Review of Molecular Diagnostics



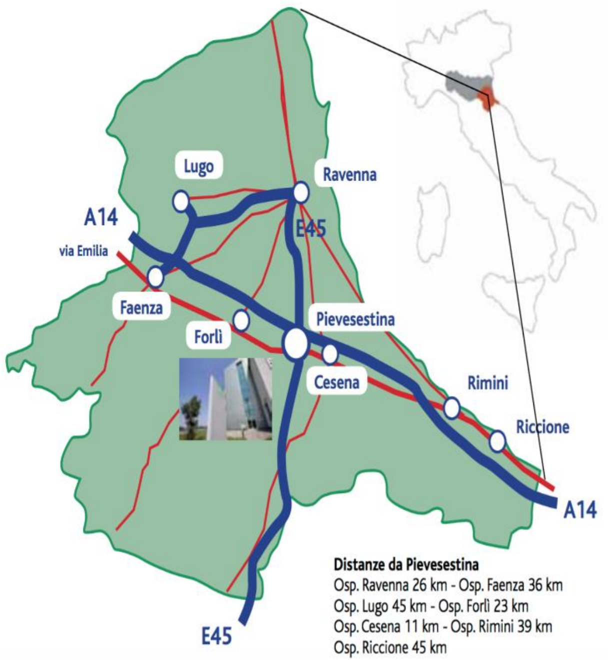
Clinical Microbiology and Infection, Volume 21 Number 4, April 2015



To cite this article: Grégory Dubourg, Didier Raoult & Florence Fenollar (2019): Emerging methodologies for pathogen identification in bloodstream infections: an update, Expert Review of Molecular Diagnostics, DOI: 10.1080/14737159.2019.1568241

The Great Romagna Area: organization of Hub Laboratory

- Central Service Laboratory was born in March 2009. This service is responsible for all diagnostics tests of Romagna Area.
- The "hub and spoke" model is as follows:
  - **7 Quick-response laboratories located in 7 Decentralized Hospitals** (open 24h/7 days)
  - **1 PVS Central Laboratory HUB** organized in 3 operating units:
    - Clinical Pathology, **Microbiology** and Medical Genetics
  - 21 million tests/year (1.000.000 Microbiology)
  - Monday - Friday (8:00 to 18:30) Saturday – Sunday (8:00 to 16:00)



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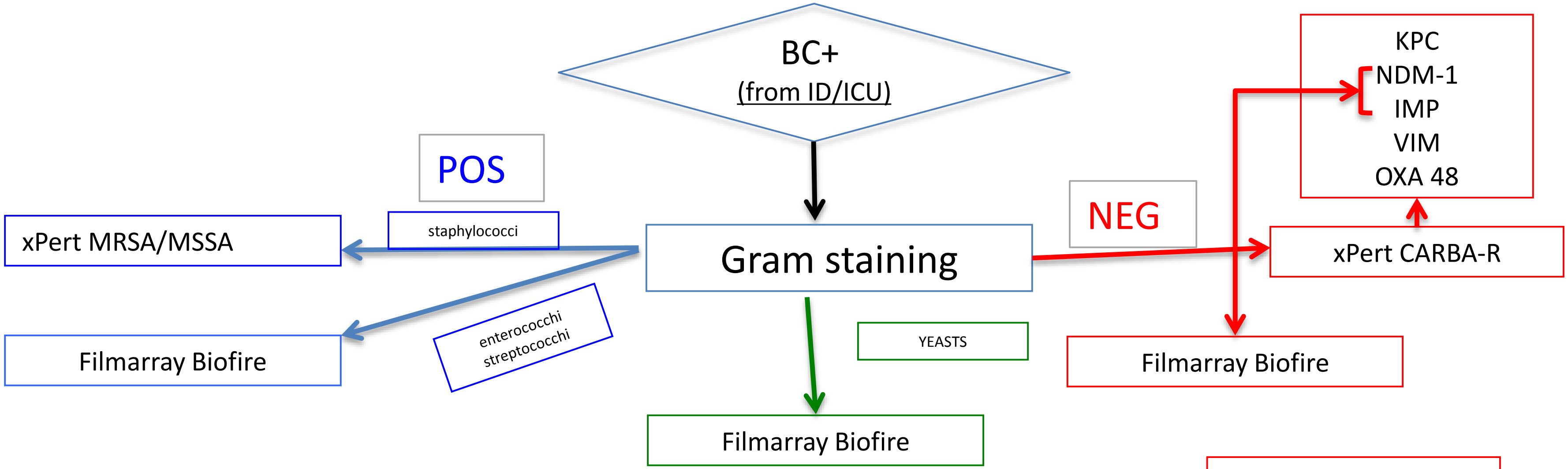
Still OPEN ISSUES

- **BLOOD CULTURES**
  - Incubation h 24/7 (spokes)
  - Only the POSITIVE are transferred to the HUB
  - Opening HOURS differ from HUB to SPOKE
  - **New regulatory rule for the accreditation of Microbiology Labs states that "evidence must be given that the BC workflow is not interrupted…."**

Still OPEN ISSUES..... Answers...

- BLOOD COLTURES
  - Implement more BC incubation slots in SPOKES
  - MALDI TOF
  - The “emo-FAST” algorithm
  - Hub open 7/7 – 12/24
  - Molecular (easy to use Film Array...) techniques in SPOKES



xPert CARBA-R:
CPR (non ID)

xPert MRSA/MSSA: MRSA/MSSA e CoNS

Filmarray Biofire:
- *S.aureus*
- CoNS
- *Enterococcus* spp.
  Streptococcus spp.
- *S.pneumoniae*
- *S.pyogenes*
- *S.agalactiae*
- *L. monocytogenes*
- mecA
- vanA/vanB

Filmarray Biofire:
- *C.albicans*
- *C.glabrata*
- *C.krusei*
- *C.parapsilosis*
- *C.tropicalis*

Filmarray Biofire:
- *Acinetobacter baumanni*
- Enterobacteriaceae
- *Enterobacter cloacae*
- *Proteus* spp.
- *E.coli*
- *K.pneumoniae*
- *K.oxytoca*
- *P.aeruginosa*
- *Serratia* spp.
- *N.meningitidis*
- *H.influenzae*
- KPC

EMO FAST 1.0 (01.01.2016 – 30.04.2017)

- 140 patients (total BC 22932: 0.6%)
  - 47 positive
  - 93 negative (66%)
  - All the "FAST RESULTS" were in agreement with those of the standandard procedure
  - Average TAT: 2 hours & 13 minutes (from the BC bottle positivity detection)

Comparison of 'time to detection' values between BacT/ALERT VIRTUO and BacT/ALERT 3D instruments for clinical blood culture samples

Francesco Congestrì[a,*], Maria Federica Pedna[a], Michela Fantini[a], Michela Samuelli[a], Pasqua Schiavone[a], Arianna Torri[a], Stefania Bertini[a], Vittorio Sambri[a,b]

- 3063 Positive BCs (routine)
  - 1601 from 01.01.15 to 31.03.15: 3D
  - 1462 from 01.12.15 to 31.03.16: VIRTUO
  - NO polymicrobial growth

International Journal of Infectious Diseases 62 (2017) 1–5

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VIRTUO vs BacT/ALERT 3D: TTD

		VIRTUO		BTA 3D	
GROUP	MICROORGANISMS INCLUDED IN EACH GROUP	N° of isolates	% of frequency	N° of isolates	% of frequency
CoNS	*Staphylococcus epidermidis*	266	59%	378	64%
	Staphylococcus hominis	86	19%	87	15%
	Staphylococcus capitis	51	11%	52	9%
	Staphylococcus haemolyticus	21	5%	33	6%
	Staphylococcus warneri	8	2%	13	2%
	other CoNS species	19	4 %	27	4%
Escherichia coli	*Escherichia coli*	376	100%	423	100%
Enterobacteriaceae (other than *E. coli*)	*Klebsiella pneumoniae*	116	46%	64	52%
	Klebsiella oxytoca	34	13%	1	1%
	Serratia marcescens	25	10%	7	6%
	Proteus mirabilis	25	10%	14	11%
	Enterobacter cloacae	22	9%	16	13%
	Enterobacter aerogenes	6	2%	1	1%
	Raoultella planticola	10	4%	2	2%
	Providencia stuartii	2	1%	4	3%
	Morganella morganii	2	1%	8	6%
	Proteus vulgaris	1	0%	5	4%
	other species	9	4%	2	2%
Staphylococcus aureus	*Staphylococcus aureus*	139	100%	163	100%
Viridans group streptococci	*Streptococcus pneumoniae*	36	37%	40	45%
	Streptococcus anginosus	23	24%	4	4%
	Streptococcus mitis	20	21%	10	11%
	Streptococcus gallolyticus	5	5%	13	15%
	Streptococcus parasanguinis	4	4%	5	6%
	Streptococcus sanguinis	3	3%	5	6%
	Aerococcus viridans	3	3%	-	-
	Streptococcus salivarius	1	1%	5	6%
	Streptococcus infantarius	-	-	4	4%
	Streptococcus thermophilus	-	-	2	2%
	other species	2	2%	1	1%
Enterococcus spp.	*Enterococcus faecalis*	39	60%	78	76%
	Enterococcus faecium	24	37%	23	22%
	Enterococcus avium	2	3%	0	0%
	Enterococcus casseliflavus	-	-	2	2%
Pseudomonas aeruginosa	*Pseudomonas aeruginosa*	46	100%	42	100%
Candida species	*Candida albicans*	24	65%	35	54%
	Candida glabrata	8	21%	19	29%
	Candida parapsilosis	5	14%	11	17%

Table 1 Frequency of isolation of microorganisms for each of two systems.

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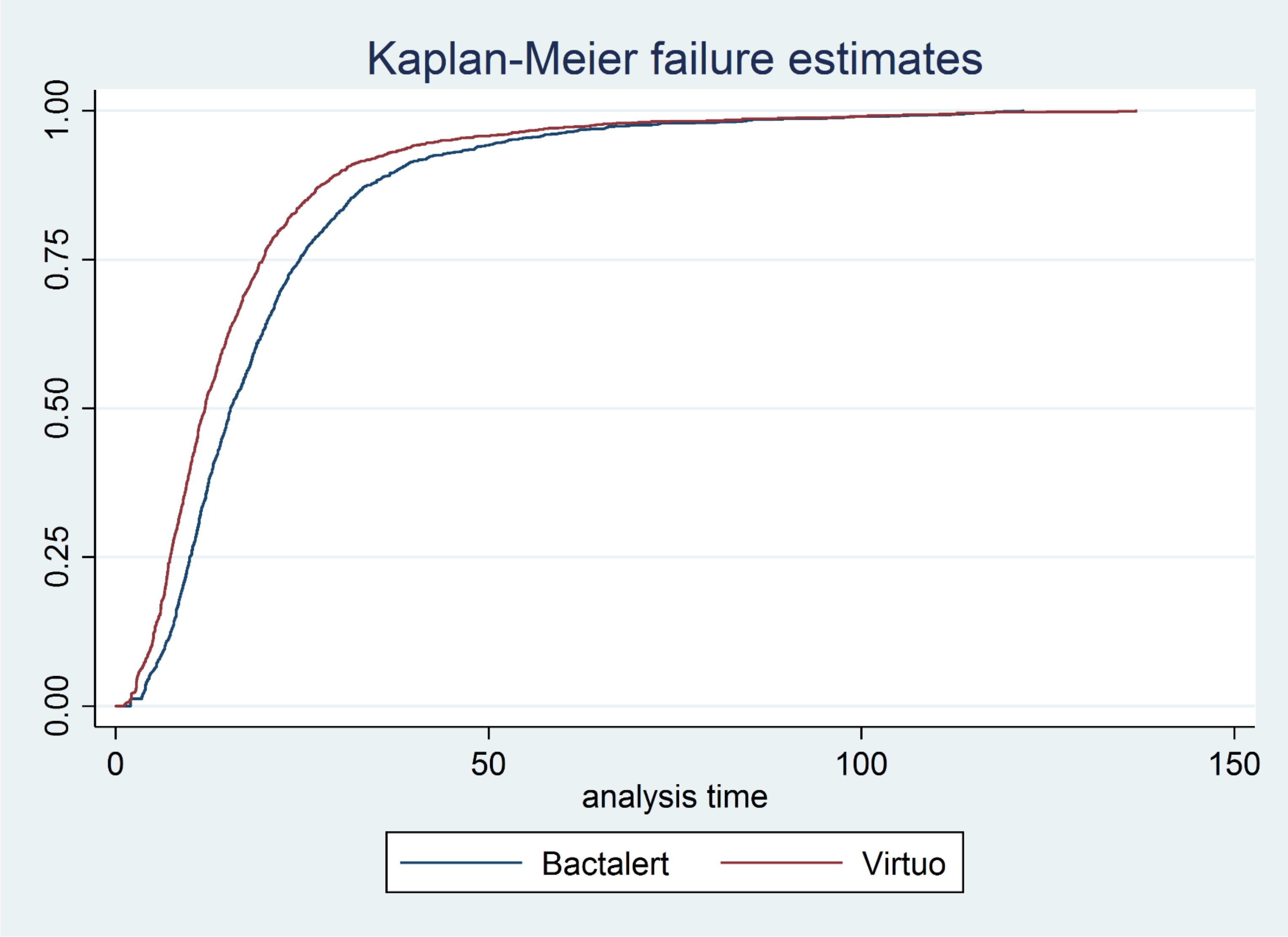
VIRTUO vs BacT/ALERT 3D: TTD



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VIRTUO vs BacT/ALERT 3D: TTD

Microorganisms categories	BTA 3D			VIRTUO			Median TTD difference (hours and minutes between VIRTUO and BTA 3D)	Variation (%)	P-value
	N° positive bottles	Frequency of isolation over the total number of bottles evaluated	Median TTD	N° positive bottles	Frequency of isolation over the total number of bottles evaluated	Median TTD			
CoNS	590	36.9%	22h42m	451	30.8%	18h35m	4hours 7 min*	-18,1%	**< 0.0001**
Escherichia coli	423	26.4%	10h36m	376	25.7%	8h35	2hours 1 min*	-20,8%	**< 0.0001**
Enterobacteriaceae (other than E. coli)	124	7.7%	11h02m	252	17.4%	8h	3hours 2 min*	-29,8%	**< 0.0001**
Staphylococcus aureus	163	10.2%	13h54m	139	9.5%	12h50m	1hour 4 min*	-12,2%	**0.035**
Viridans group streptococci	89	5.6%	13h	97	6.6%	11h	2 hours*	-16%	**0.0303**
Enterococcus species	103	6.6%	10h42m	65	4.4%	11h54m	-1 hour 12 min	11,2%	0.96
Pseudomonas aeruginosa	42	2.5%	16h30m	46	3.1%	14h10	2hours 20 min	-13.9%	0.14
Candida species	65	4.1%	22h48m	37	2.5%	20h47m	2hours 1 min	-9,2%	0.431

Table 2 Median TTD difference and Variation expressed as percentage between the two system

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Risk-assessment may improve selection of patients with suspected sepsis for rapid diagnostics

Logan Ward[1,2], Michela Fantini[3], Vittorio Sambri[3], Steen Andreassen[1,2]

1. Treat Systems ApS, Aalborg, Denmark; 2. Aalborg University, Aalborg, Denmark; 3. Greater Romagna Area Hub Laboratory, Cesena, Italy

24 April 2017

27th ECCMID Vienna, Austria 22 – 25 April 2017

AALBORG UNIVERSITY DENMARK

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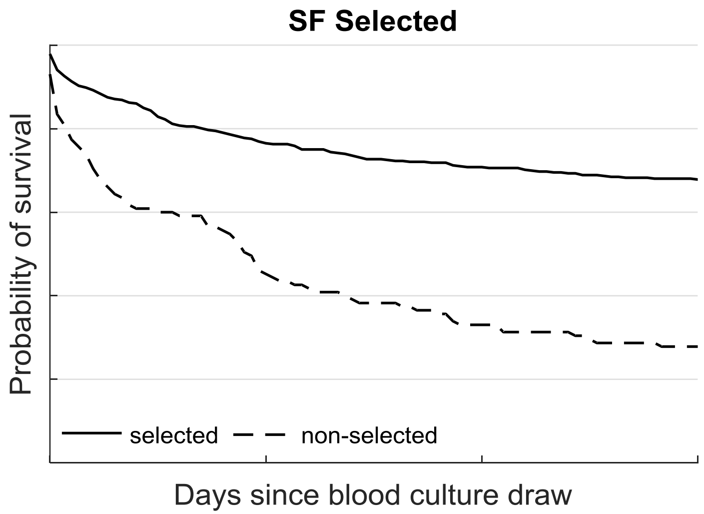
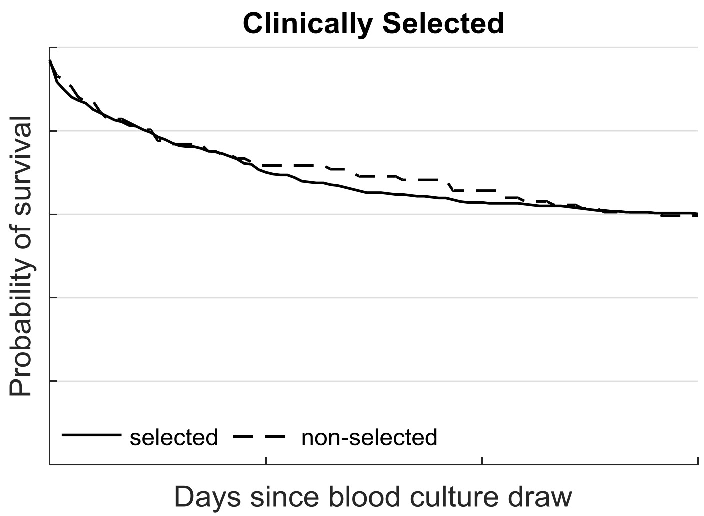


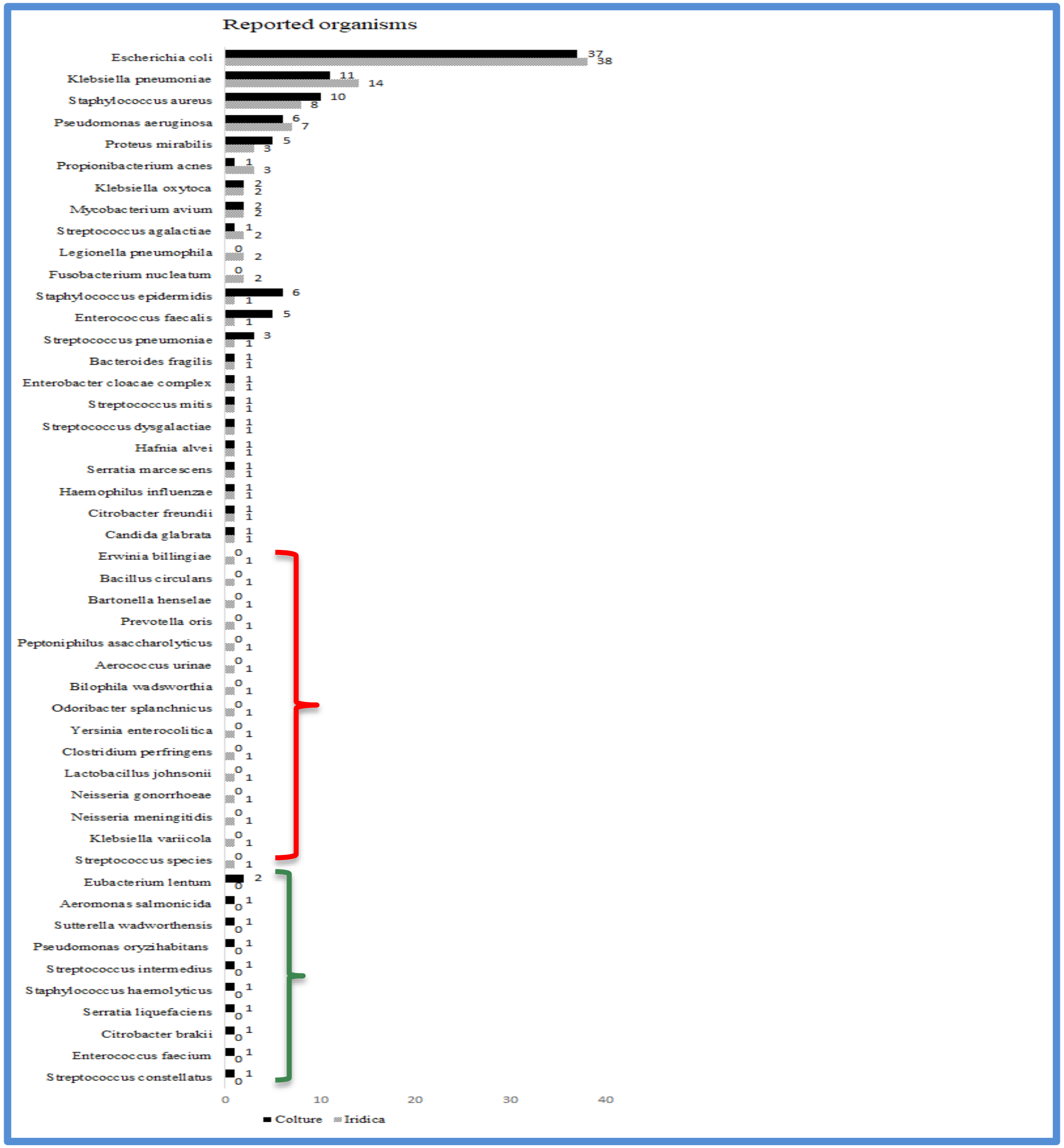


Upper panel shows SF selected and non-selected. Lower panel shows Clinically selected and non-selected.

Rapid Diagnosis of Bloodstream Infections in the Critically Ill: Evaluation of the Broad-Range PCR/ESI-MS Technology

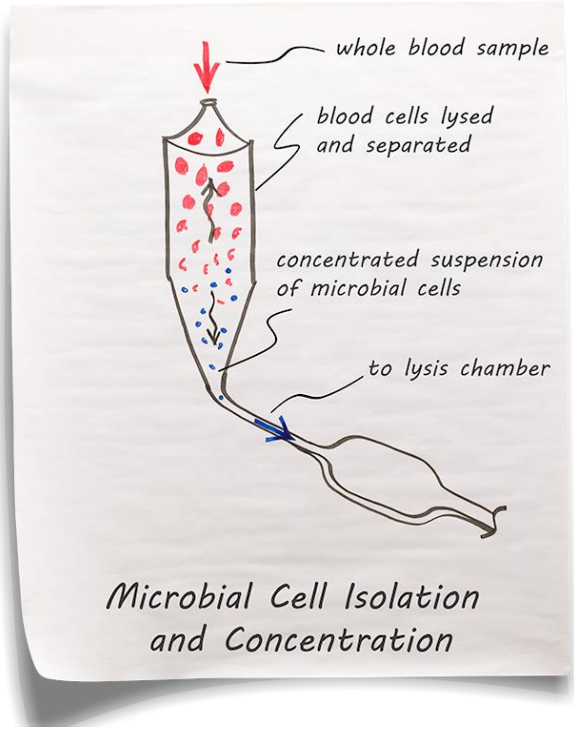
- 300 whole blood samples were prospectively collected between May 1st 2016 and December 31st 2016 from consenting patients who presented to one of the ER units participating in the study
- The chief selection criterion was a clinical suspicion of sepsis
- PCR/ESI-MS and the microbiology testing, including incubation, were performed. The IRIDICA BAC BSI Assay and standard-of-care testing were performed blindly to one another's results. The reports from the microbiology testing were used in this study as the comparative method to evaluate the IRIDICA System.

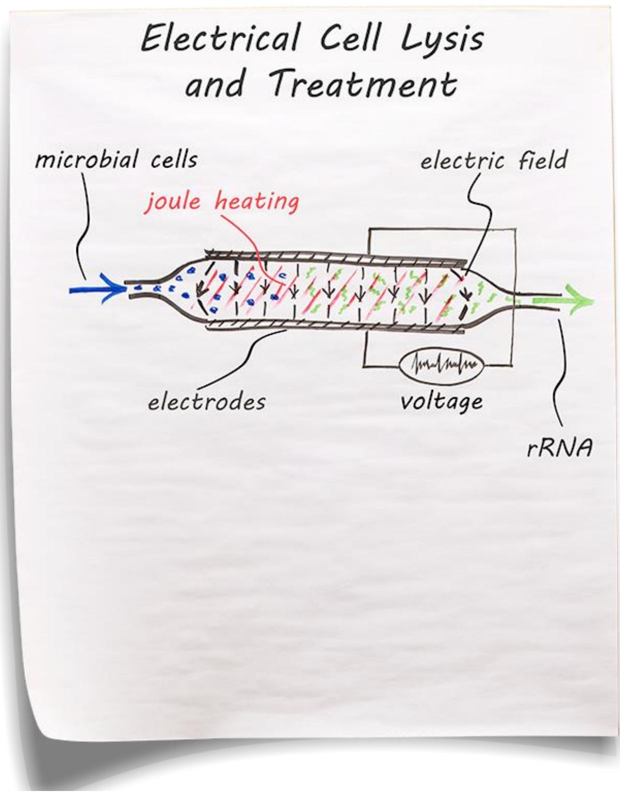
Tassinari M. et al.
PLoS One. 2018 May 15;13(5):e0197436.

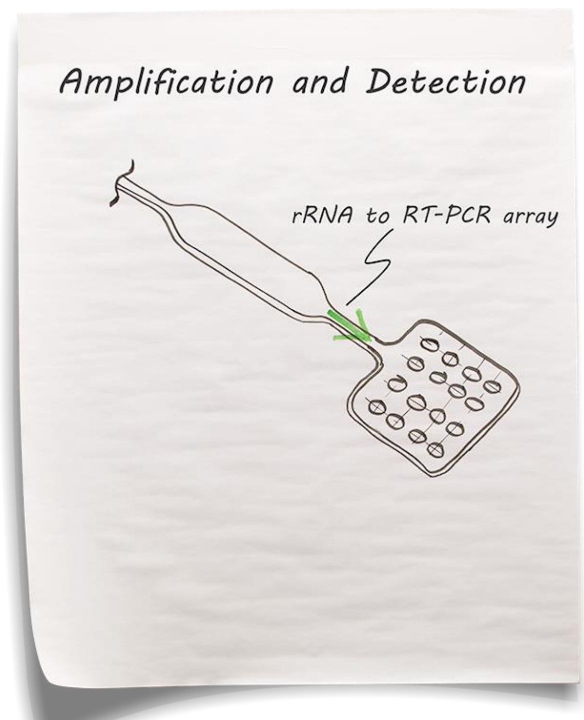

Reported organisms
Escherichia coli 37 38
Klebsiella pneumoniae 11 14
Staphylococcus aureus 10 8
Pseudomonas aeruginosa 6 7
Proteus mirabilis 5 3
Propionibacterium acnes 1 3
Klebsiella oxytoca 2 2
Mycobacterium avium 2 2
Streptococcus agalactiae 1 2
Legionella pneumophila 0 2
Fusobacterium nucleatum 0 2
Staphylococcus epidermidis 6 1
Enterococcus faecalis 5 1
Streptococcus pneumoniae 3 1
Bacteroides fragilis 1 1
Enterobacter cloacae complex 1 1
Streptococcus mitis 1 1
Streptococcus dysgalactiae 1 1
Hafnia alvei 1 1
Serratia marcescens 1 1
Haemophilus influenzae 1 1
Citrobacter freundii 1 1
Candida glabrata 1 1
Erwinia billingiae 0 1
Bacillus circulans 0 1
Bartonella henselae 0 1
Prevotella oris 0 1
Peptoniphilus asaccharolyticus 0 1
Aerococcus urinae 0 1
Bilophila wadsworthia 0 1
Odoribacter splanchnicus 0 1
Yersinia enterocolitica 0 1
Clostridium perfringens 0 1
Lactobacillus johnsonii 0 1
Neisseria gonorrhoeae 0 1
Neisseria meningitidis 0 1
Klebsiella variicola 0 1
Streptococcus species 0 1
Eubacterium lentum 2 0
Aeromonas salmonicida 1 0
Sutterella wadworthensis 1 0
Pseudomonas oryzihabitans 1 0
Streptococcus intermedius 1 0
Staphylococcus haemolyticus 1 0
Serratia liquefaciens 1 0
Citrobacter brakii 1 0
Enterococcus faecium 1 0
Streptococcus constellatus 1 0
0 10 20 30 40
Colture Iridica

PROs & CONs

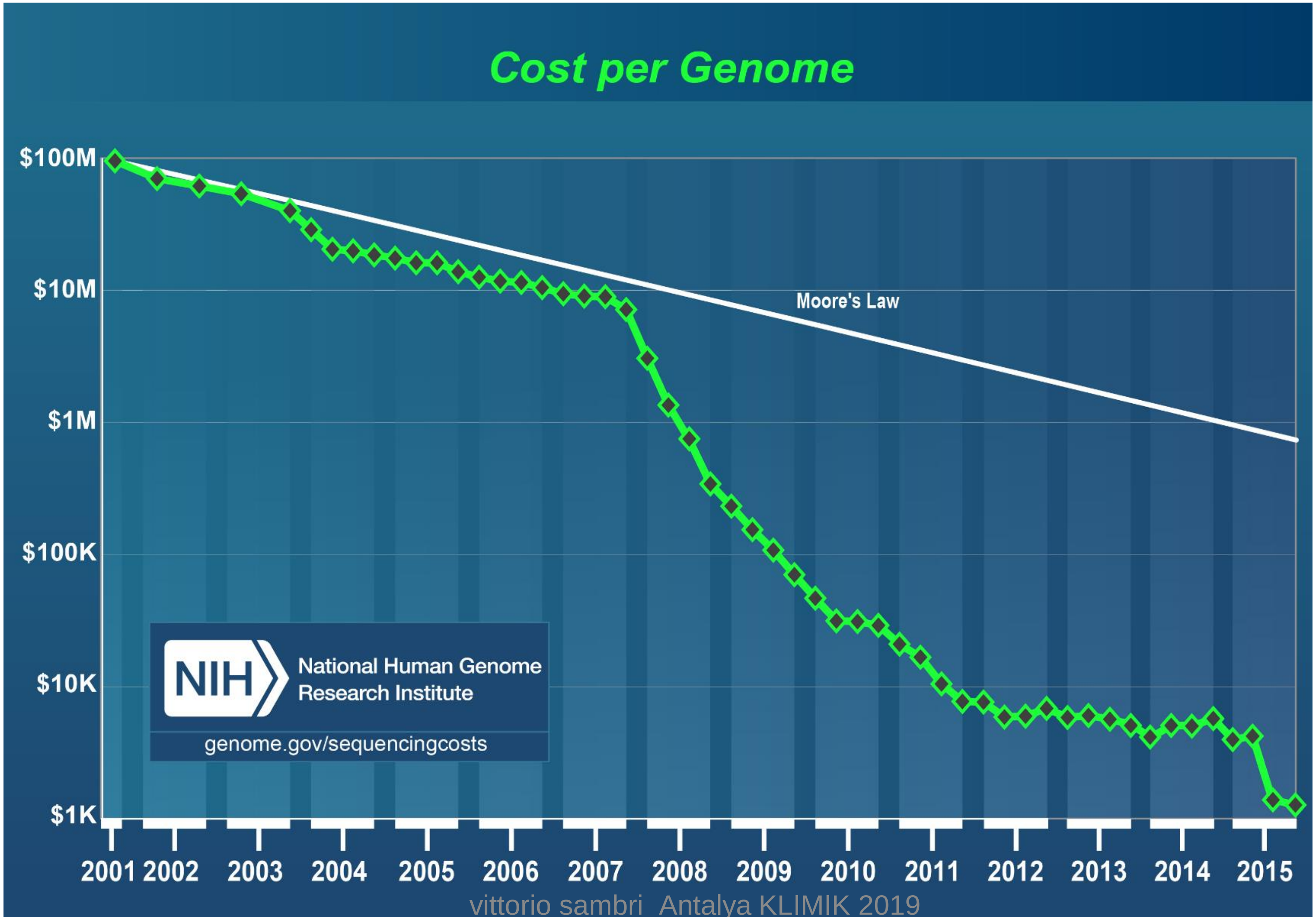
- High sensitivity (800 spp.)
- High specificity
- Clinical Interpretation
- Complex instrumentation
- Need to be laboratory based (logistic)
- Limited number of specimens/run
- Cost/efficacy







preparation method that combines centrifugal separation and electrical lysis of pathogen cells. This provides a PCR-ready lysate while avoiding the complexities encountered with conventional nucleic acid extraction and purification



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march 15

Whole genome sequencing, abbattimento dei costi …

History

1970s:	DNA sequencing starts
1990:	The “Human Genome Project” starts
2003:	First human genome fully sequenced
2012:	UK announces sequencing of 100K genomes
2015:	USA announces sequencing of 1M genomes

$$$

$3B:	Human Genome Project
$250K:	Illumina (2008)
$5K:	Complete Genomics (2009), Illumina (2011)
$1K:	Illumina (2014)

4

WGS for bacterial genomes
1990, 3.000.0000 US $
1995, 500.000 US $
2017, 30-100 US $

Whole-Genome Sequencing of Bacterial Pathogens: the Future of Nosocomial Outbreak Analysis

Scott Quainoo,[a] Jordy P. M. Coolen,[b] Sacha A. F. T. van Hijum,[c,d]
Martijn A. Huynen,[c] Willem J. G. Melchers,[b] Willem van Schaik,[e]
Heiman F. L. Wertheim[b]

Recently, whole-genome sequencing (WGS) of pathogens has become more accessible and affordable as a tool for genotyping.

Analysis of the entire pathogen genome via WGS could provide unprecedented resolution in dis-criminating even highly related lineages of bacteria and revolutionize outbreak anal-ysis in hospitals.

Nevertheless, clinicians have long been hesitant to implement WGS in outbreak analyses due to the expensive and cumbersome nature of early se- quencing platforms. Recent improvements in sequencing technologies and analysis tools have rapidly increased the output and analysis speed as well as reduced the overall costs of WGS.

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When I say “we”. … I mean <u>THEM</u>

U.O. MICROBIOLOGIA

Pievesestina

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EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale della Romagna