Novel and Emerging Technologies in Molecular Microbiology: Diagnostic Principles and Practice

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Goals of Presentation

- Review what we mean by molecular diagnostics
  - Why use molecular diagnostics versus traditional laboratory methods
- Review how molecular diagnostics have evolved
  - Tuberculosis
  - Sepsis
  - Sexually transmitted infections
- Describe the next wave of molecular diagnostics
- Comment on where molecular diagnostics are being used.

Molecular Diagnostics - Definition

* The application of nucleic acid hybridization techniques (DNA probes), polymerase chain reaction (PCR), other nucleic acid amplification test (NAAT) methods, nucleic acid sequence analysis, or mRNA detection methods (host response markers) for the rapid and accurate identification of infectious disease agents directly in clinical specimens.

Molecular Diagnostics - Goals

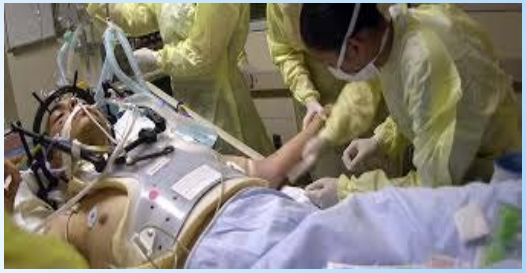
* Reduce the time to identification of infectious agents so that appropriate therapy can be initiated to maximize patient outcomes.
* Optimize workflow in the laboratory
* Bring diagnostic methods to rural or remote areas where microbiology services were previously unavailable to improve healthcare globally

Why Use Molecular Diagnostics?

- Conventional detection methods are too slow
  - Organisms causing sepsis need to be detected quickly to guide appropriate therapy
  - Improve diagnosis of tuberculosis (1 hour for PCR vs 3-4 weeks for culture results)
- Conventional methods lack sensitivity
  - Replace inaccurate rapid antigen influenza tests (low sensitivity) to improve antiviral use
- Conventional tests do not exist
  - Detection of Noroviruses to implement infection control measures during outbreaks

Key Questions When Using Molecular Diagnostics to Guide Therapy

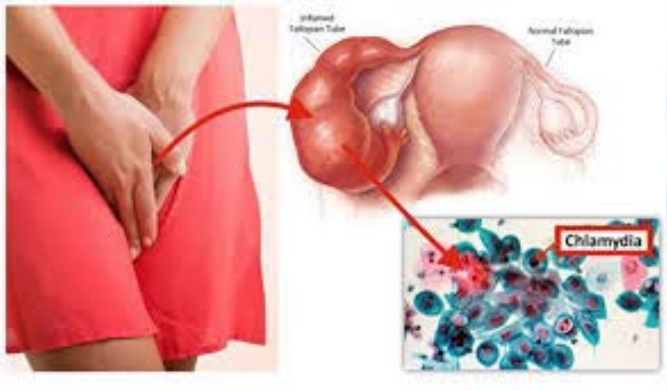
- **Sepsis**
  - Gram-positive versus Gram-negative bacteria
  - Are antimicrobial resistance genes present
- **Sexually transmitted infections**
  - Chlamydia, gonorrhea, herpes, mycoplasma, trichomonas, other (the list keeps getting longer)
- **Respiratory tract infections**
  - Bacterial, viral, or non-infectious
- **Meningitis/encephalitis**
  - Bacterial, viral, fungal, parasitic
- **Tuberculosis**
  - Pan-susceptible to drugs, MDR, XDR



Is diagnosis and treatment of these infections different today vs 10 years ago?

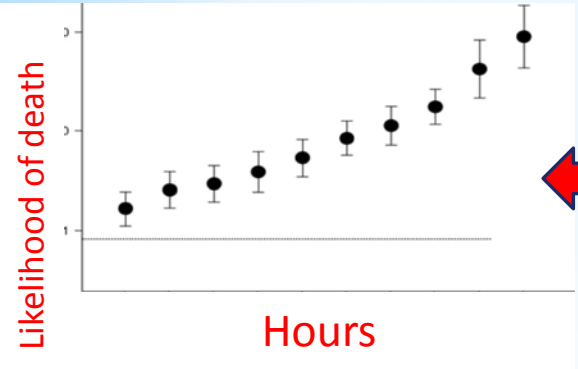
Sepsis/bloodstream infection

Tuberculosis



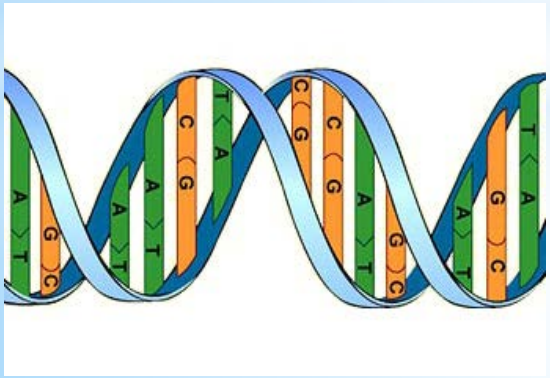
Chlamydia trachomatis

Diagnosis of Sepsis



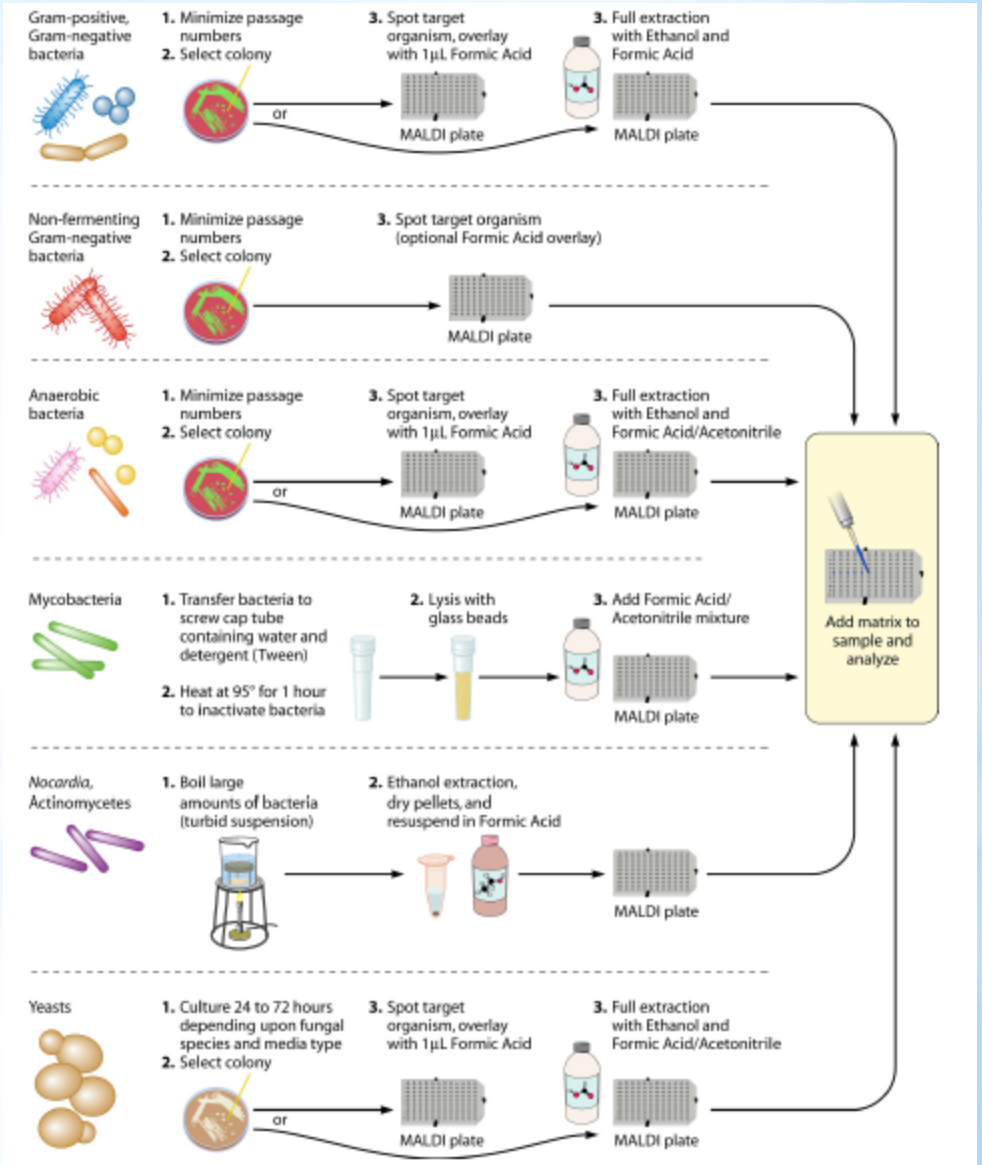
The issue: Mortality increases ~6% for each hour of delay before starting effective treatment for sepsis

Culture methods need 24 hours to detect growth in a blood culture bottle and 6-48 hours to identify the organism and determine its antibiotic susceptibility pattern

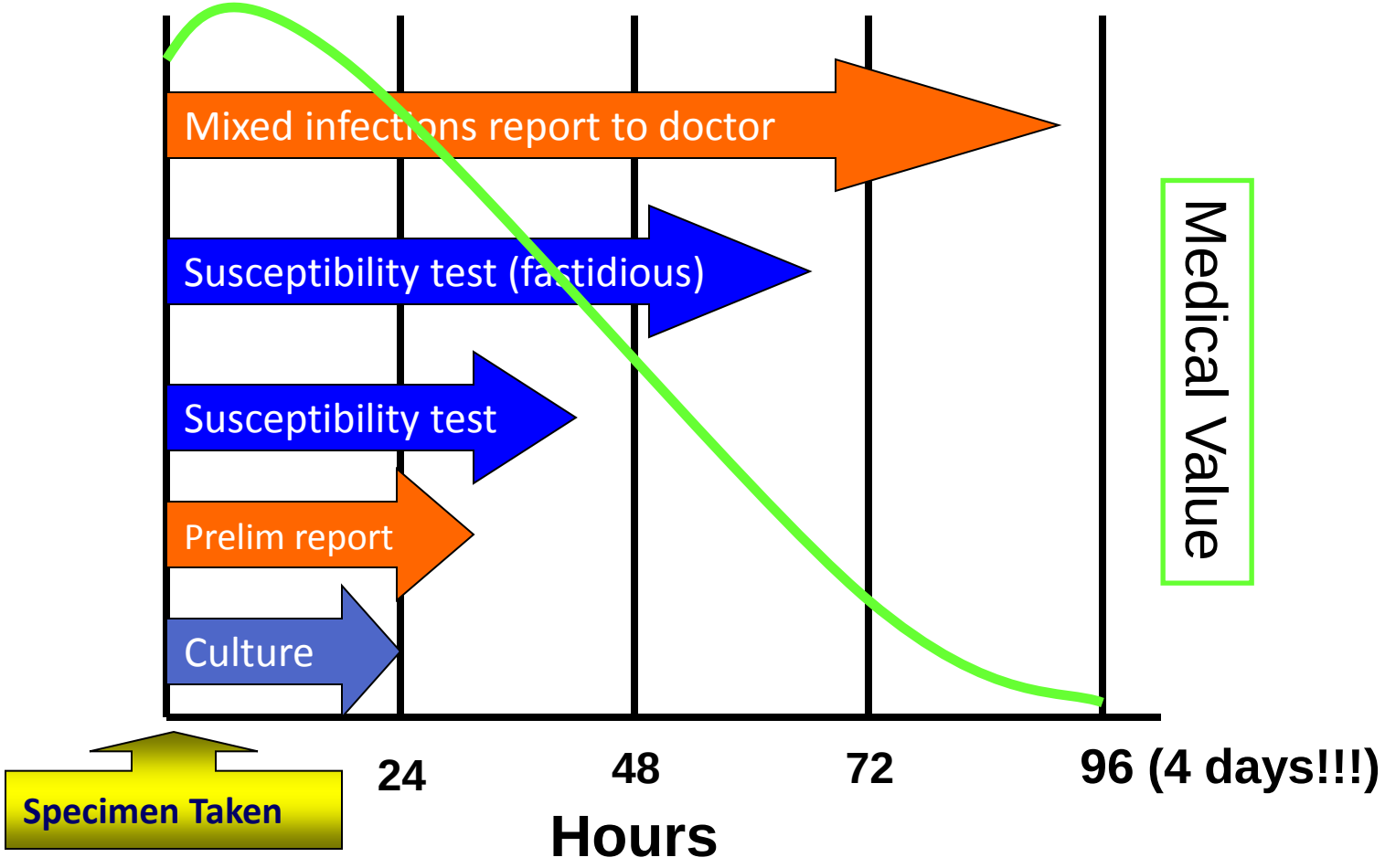


Molecular methods can give results in 1-2 hrs for detecting bacteria in blood culture bottles, and 2-4 hrs for direct detection bacteria and *Candida* spp. in blood

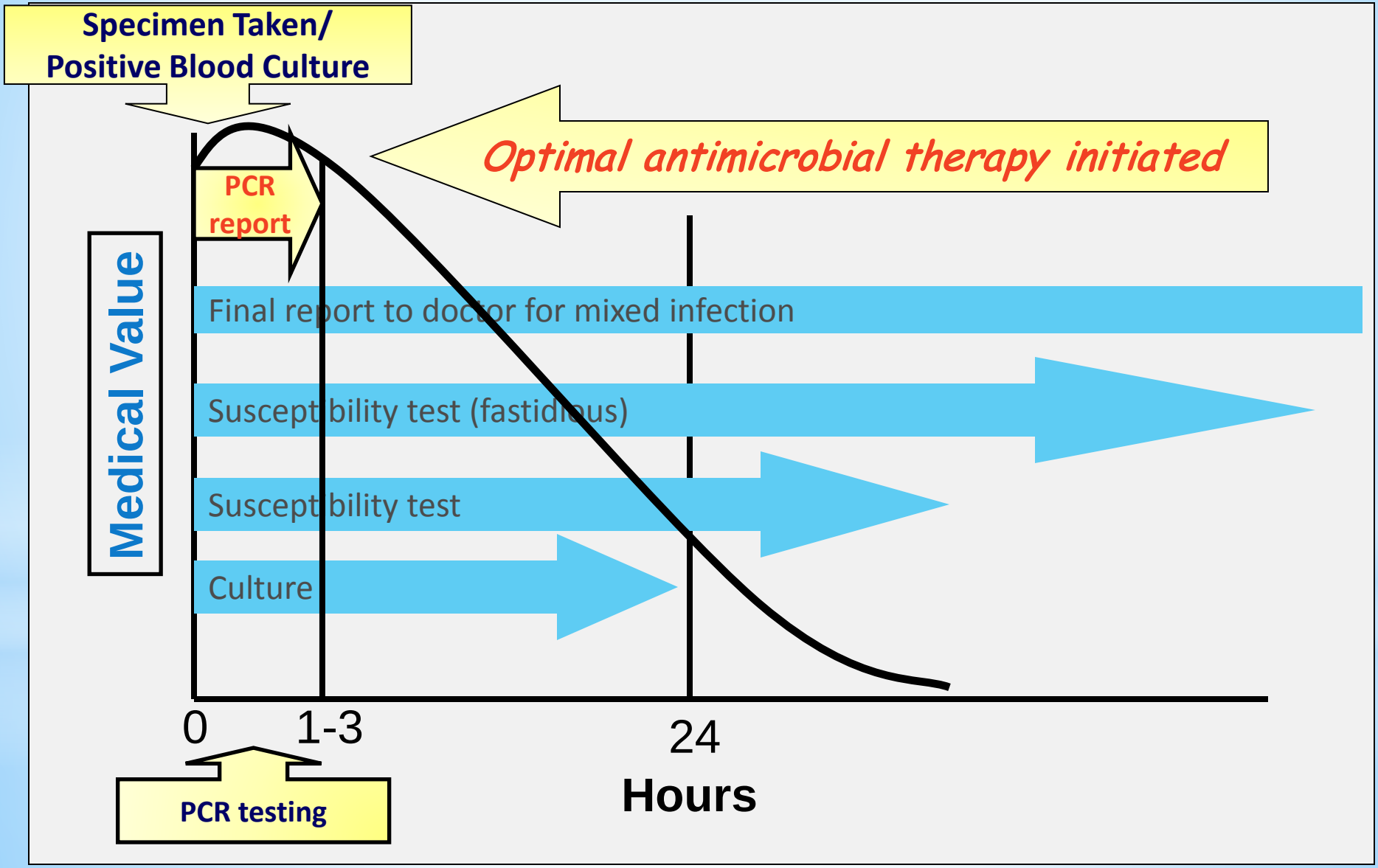
Blood culture methods



Need to Change the Slow Delivery of Results With Low Medical Impact

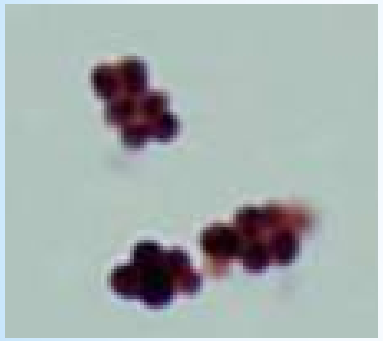


Molecular Methods Change the Paradigm



Examples of Molecular Diagnostics for Blood Cultures: *S. aureus*, MRSA, Coagulase Negative Staphylococci

Gram + cocci in clusters



PCR testing Xpert MRSA/SA (~1 hour)

PCR/Array with nanoprobes: Nanosphere (3 hours)

Filmarray (BioFire): *S. aureus*, *mecA* resistance genes (1 hour)

MALDI-TOF ID

All these methods provide bacterial identifications in 1-3 hours, So targeted therapy can be started

Impact of an Assay That Enables Rapid Determination of *Staphylococcus* Species and Their Drug Susceptibility on the Treatment of Patients with Positive Blood Culture Results

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY OCTOBER 2010, VOL. 31, NO. 10

Mark Parta, MD; Melanie Goebel, BS; Jimmy Thomas, MD; Mahsa Matloobi, MD; Charles Stager, PhD; Daniel M. Musher, MD

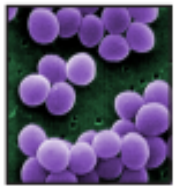
TABLE 2. Data on Drug Therapy for Patients with Bacteremia due to Methicillin-Susceptible *Staphylococcus aureus* at the Michael E. DeBakey Veterans Affairs Medical Center in Houston, Texas (2008–2009)

Variable	PCR test (n = 12)	Culture/AST (n = 48)	P^c
Mean time to initiate MSS drug therapy, hours (Hours to appropriate Rx)	5.2	49.8	.007
Median time to initiate MSS drug therapy, hours	0	48.5	.004
Mean duration of MRS drug therapy, hours (Hours on wrong Rx)	19.7	80.7	.003
No. (%) of patients not initially treated with MRS drug	3 (25.0)	5 (10.4)	
No. (%) of patients treated with MRS drug for unrelated condition	3 (25.0)	4 (8.3)	
No. (%) of patients treated with MRS drug for staphylococcal bacteremia	6 (50.0)	39 (81.3)	.025

Getting patients on the right drug 10 times faster or off the wrong drugs 4 times faster improves outcomes

FilmArray Blood Culture Identification Panel

1 Test. 27 Targets. All in about an hour.

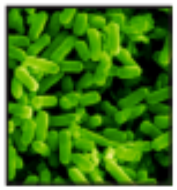


Gram + Bacteria

Enterococcus
Listeria monocytogenes

Staphylococcus
Staphylococcus aureus

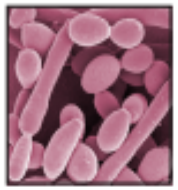
Streptococcus
Streptococcus agalactiae
Streptococcus pyogenes
Streptococcus pneumoniae



Gram – Bacteria

Acinetobacter baumannii
Haemophilus influenzae
Neisseria meningitidis
Pseudomonas aeruginosa

Enterobacteriaceae
Enterobacter cloacae complex
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus
Serratia marcescens



Yeast

Candida albicans
Candida glabrata
Candida krusei
Candida parapsilosis
Candida tropicalis

Antibiotic Resistance

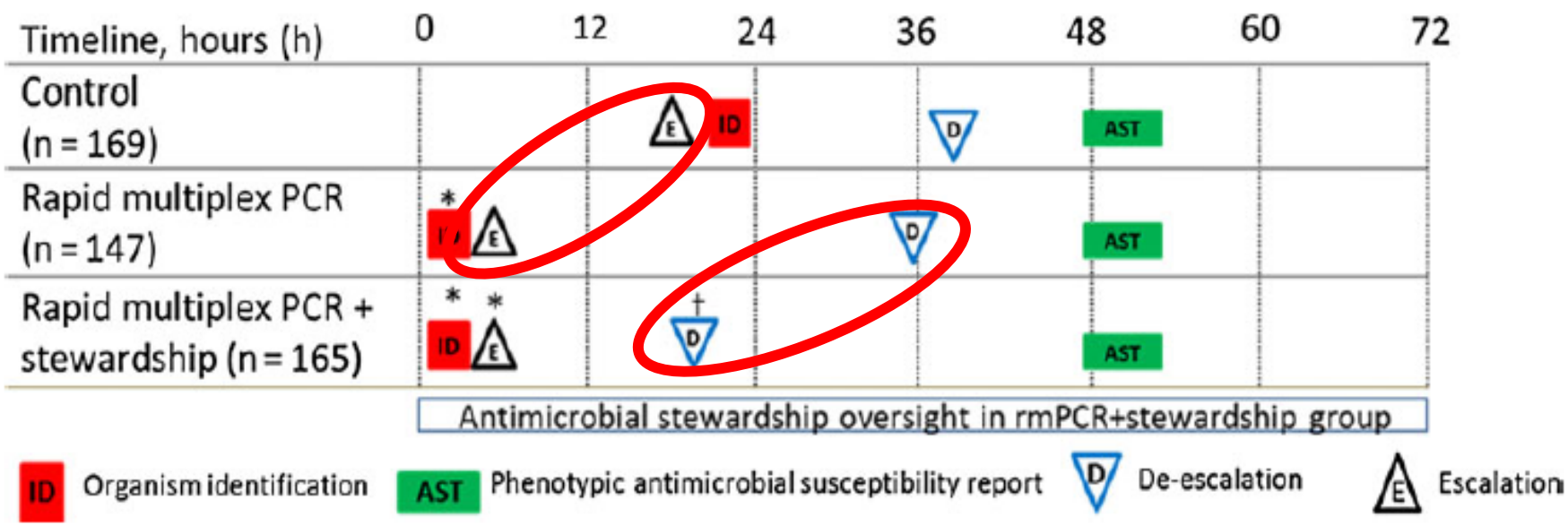
mecA - methicillin resistant
vanA/B - vancomycin resistant
KPC - carbapenem resistant

Randomized Trial of Rapid Multiplex Polymerase Chain Reaction–Based Blood Culture Identification and Susceptibility Testing

Ritu Banerjee,[1,a] Christine B. Teng,[2,a] James M. Steckelberg,[4] James P. Moriarty,[5] Nilay D. Shah,[5] Jayawant N. Mandrekar, and Robin Patel

Clinical Infectious Diseases® 2015;61(7):1071–80

Coordinated approach to Antimicrobial Stewardship important



Rapid identification needs to be paired with a call to pharmacy or stewardship team to get therapy changed if necessary

Integrating Rapid Pathogen Identification and Antimicrobial Stewardship Significantly Decreases Hospital Costs

Katherine K. Perez, PharmD; Randall J. Olsen, MD, PhD; William L. Musick, PharmD; Patricia L. Cernoch, BS; James R. Davis, PhD; Geoffrey A. Land, PhD; Leif E. Peterson, PhD; James M. Musser, MD, PhD

Table 2. Length of Stay and Cost Outcomes in Survivors[a]

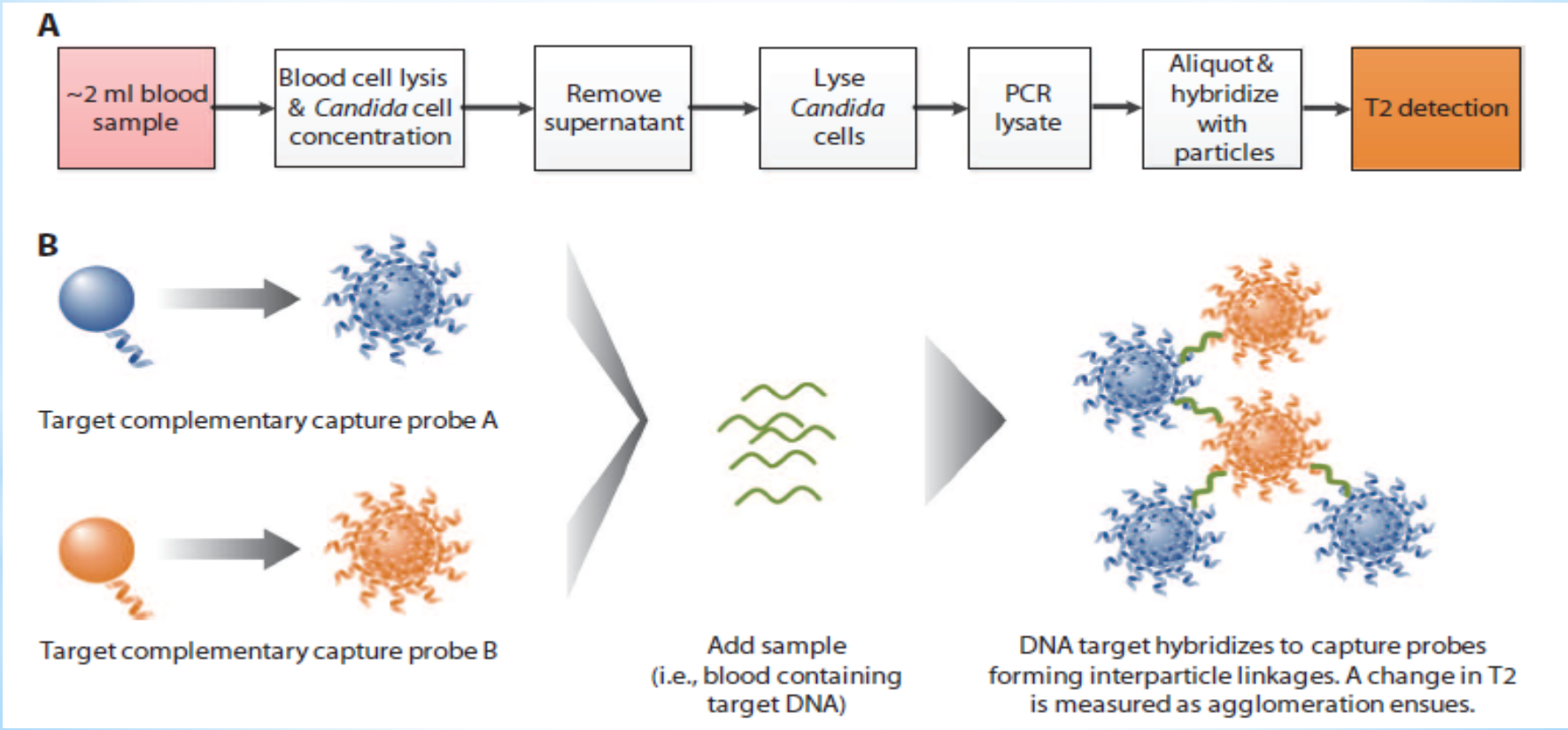
Outcome	Preintervention Cohort (n = 100)	Intervention Cohort (n = 101)	*P*
Hospital length of stay	11.9 ± 9.3	9.3 ± 7.6	.01
Hospital length of stay after BSI onset	9.9 ± 7.1	8.1 ± 6.4	.01
ICU length of stay	7.3 ± 8.5	6.3 ± 8.7	.05
ICU length of stay after BSI onset	6.1 ± 6	4.9 ± 6.7	.09
Total hospital costs	$45 709 ± $61 806	$26 162 ± $28 996	.009
MS DRG weight	2.7 ± 2.4	±1.9	54

Reducing length of stay and decreasing hospital costs are Significant drivers of new technologies plus better patient outcomes

T2 Magnetic Resonance Assay for the Rapid Diagnosis of Candidemia in Whole Blood: A Clinical Trial

Clinical Infectious Diseases® 2015;60(6):892–9

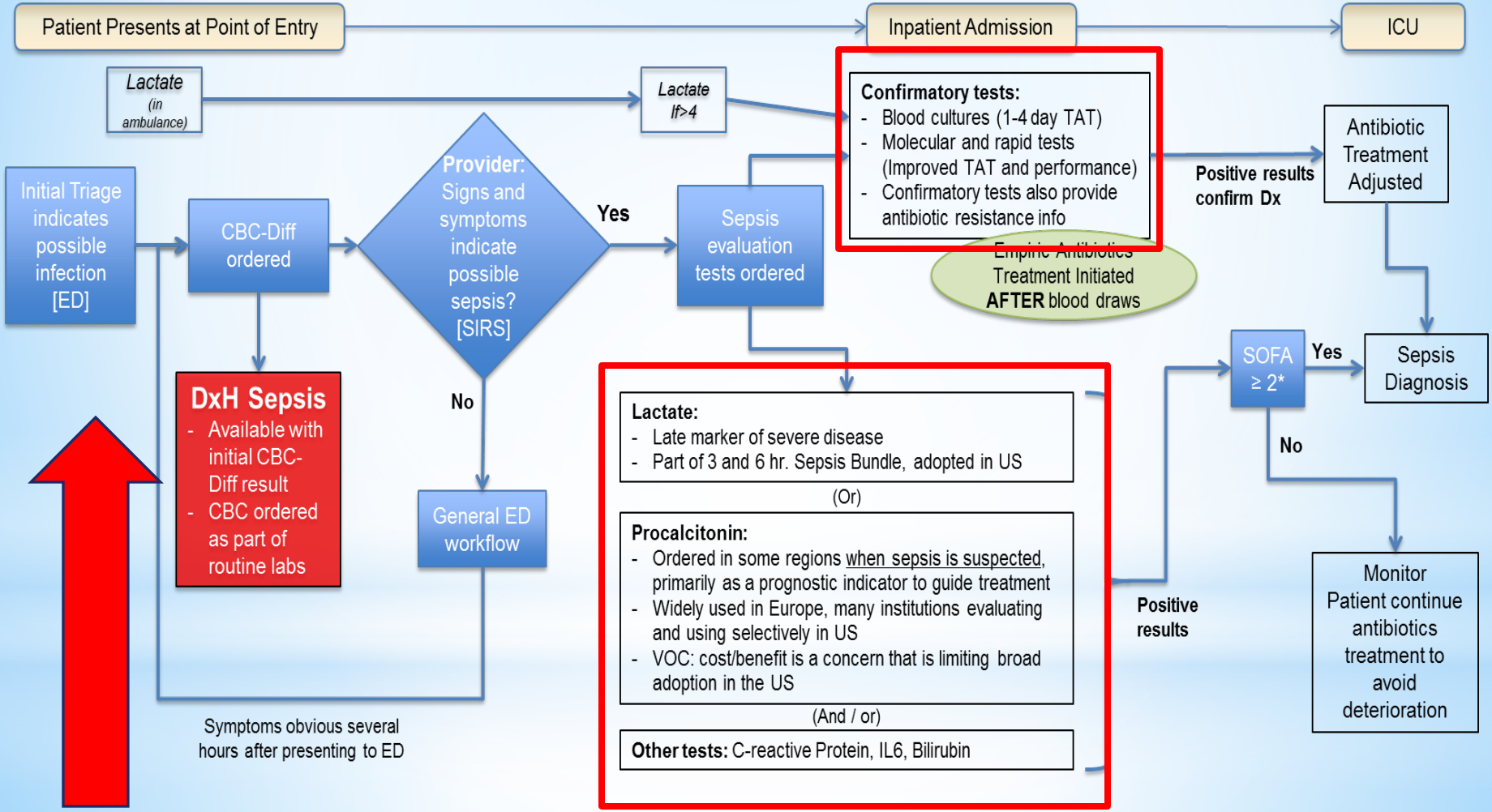
Eleftherios Mylonakis,[1] Cornelius J. Clancy,[2] Luis Ostrosky-Zeichner,[3] Kevin W. Garey,[4] George J. Alangaden,[5] Jose A. Vazquez,[6] Jeffrey S. Groeger,[7] Marc A. Judson,[8] Yuka-Marie Vinagre,[9] Stephen O. Heard,[10] Fainareti N. Zervou,[1] Ioannis M. Zacharioudakis,[1] Dimitrios P. Kontoyiannis,[11] and Peter G. Pappas[12]



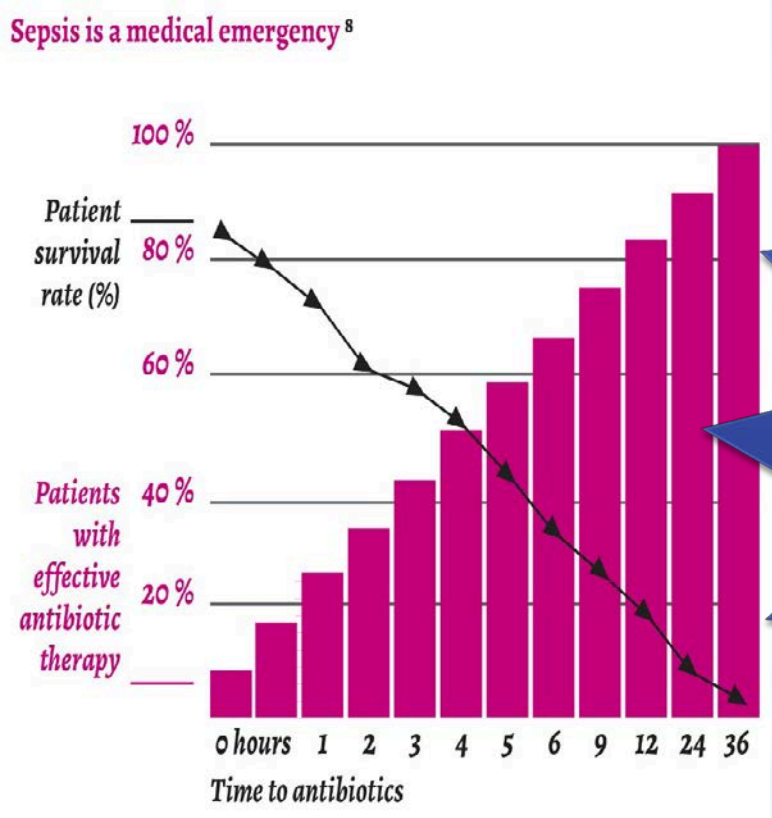
Considering a Different Approach to Sepsis

* Rather than seeking to identify an organism in the bloodstream immediately, perhaps we should determine if an infection is present at all
* Host response markers: cellular, protein, molecular

Diagnosing Sepsis BEFORE Blood Cultures are Drawn



* Innovation: Sepsis Opportunity



Sepsis

- 5 million cases per year world[illegible] and growing
- High[illegible] morbid (> 3[illegible] 10t[illegible] ng cause of death in US; 12[illegible] of deat[illegible]
- Each h[illegible] ncreases mortali[illegible]

Opportunity = Detecting more patients within critical 6-hour window for administration of antibiotics

Cur[illegible]

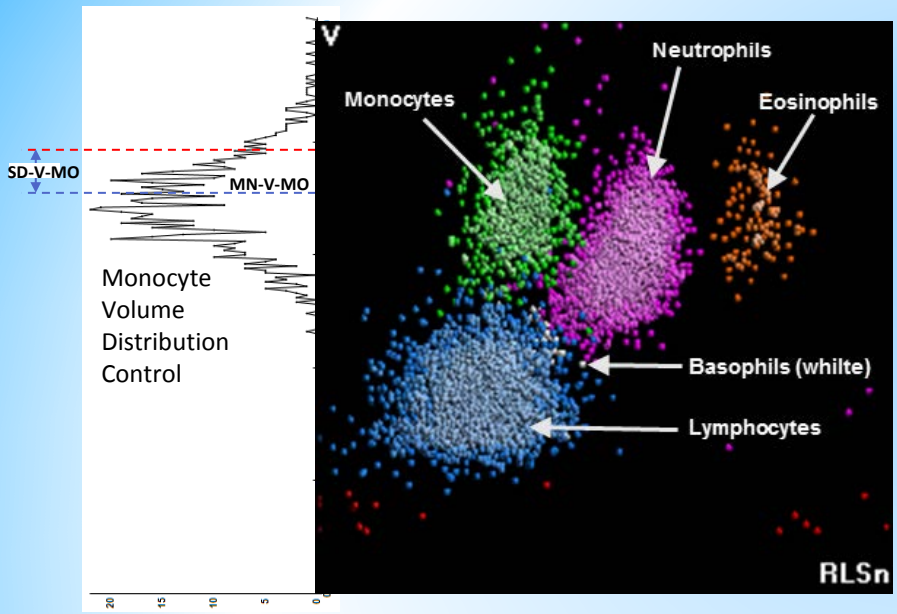
- [illegible] ose and monitor
- [illegible] com[illegible] in sepsis [illegible] sp[illegible] o diagnosis

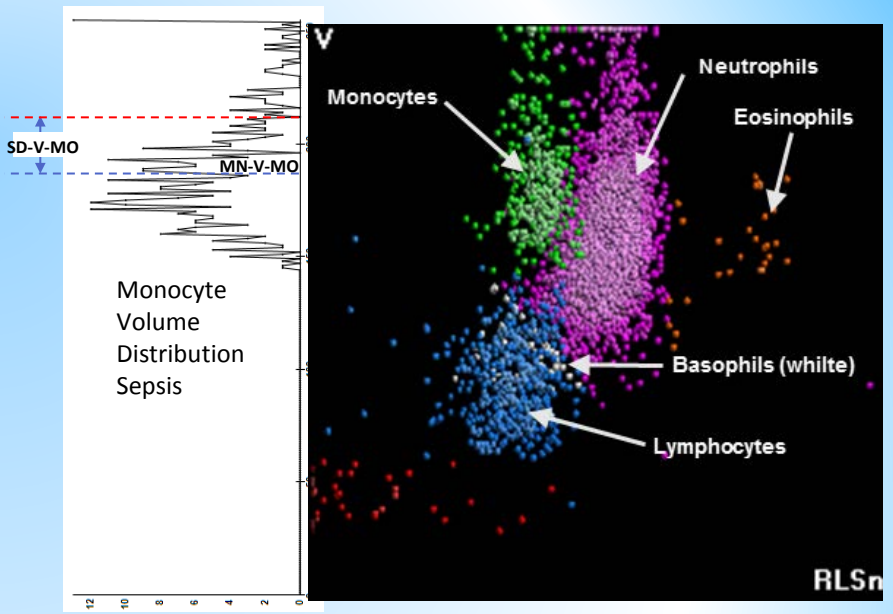
OPPORTUNITY TO REDUCE HIGHEST HEALTHCARE COSTS BY EARLIER DIAGNOSIS OF SEPSIS

* Nucleated Blood Cell Morphology Changes During Sepsis

- *Neutrophil volume increases during bacterial sepsis[1]
  - *Neutrophil volume does not change during viral infection[1]
- *Monocyte volume increases during bacterial sepsis[1]
  - *Monocytes also respond to viral infection[2]
- *Δ neutrophil volume distribution width (variation in size) is an early sign of bacterial infection[3]

1. Lee AJ, Kim SG. *Blood Res* 2013; 48:193-7.
2. Hou W, et al. *Blood* 2012;119:3128-31.
3. Chaves F, et al. *Arch Pathol Lab Med* 2006; 130:378-80.





MDW = 19.1
WBC cells x10^3= 4.73

MDW = 24.3
WBC cells x10^3 = 10.27

Non-septic

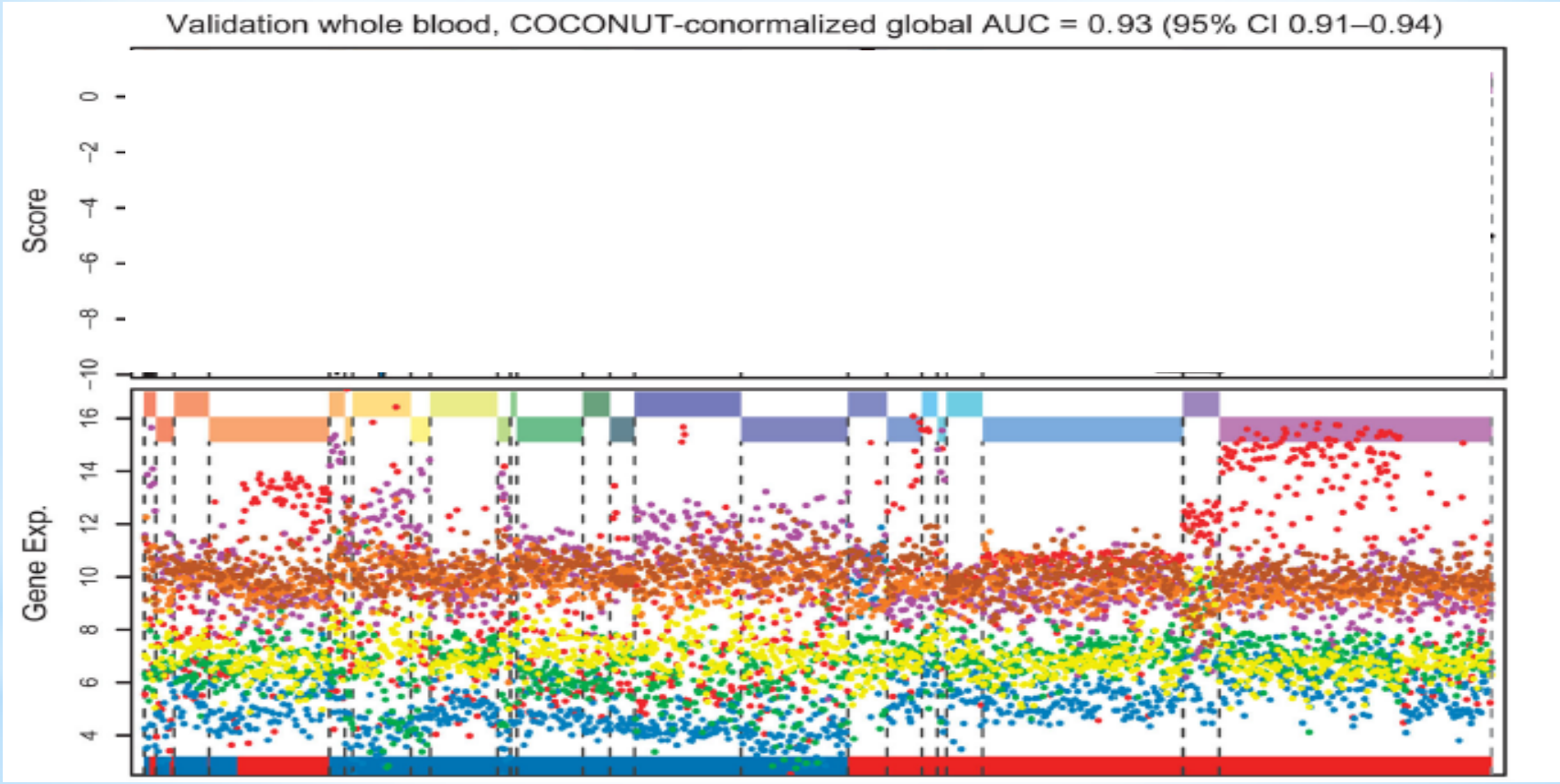
Septic

These histograms represent examples of patients diagnosed as non-septic and septic from the feasibility trial

Red dotted lines depict 1 SD from the mean

Robust classification of bacterial and viral infections via integrated host gene expression diagnostics

Timothy E. Sweeney[1,2,*], Hector R. Wong[3,4], and Purvesh Khatri[1,2,*]

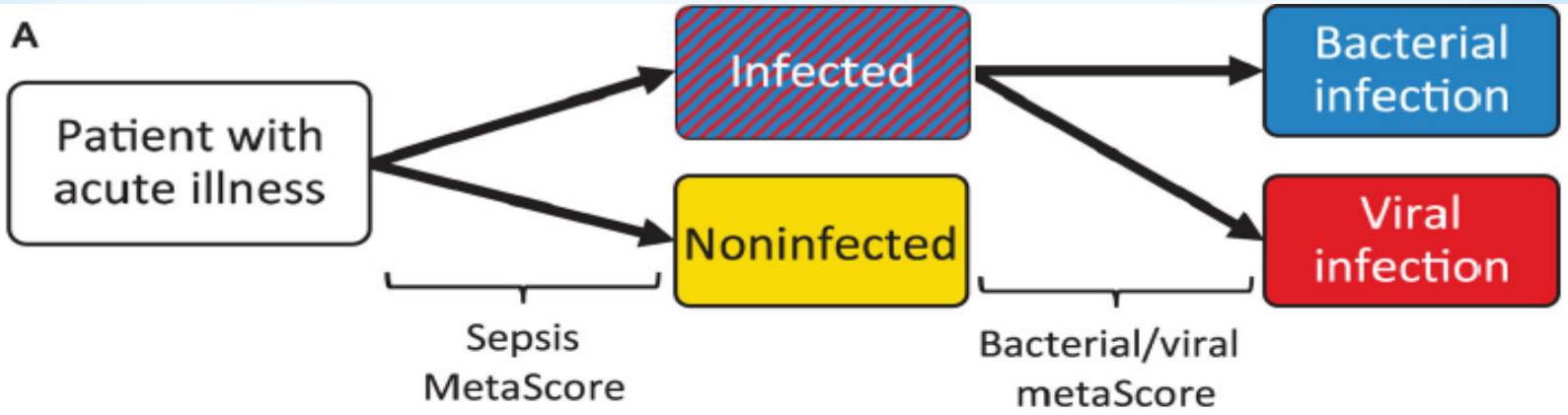


a pooled analysis of 1057 samples from 20 cohorts (excluding infants), the integrated antibiotics decision model had a sensitivity and specificity for bacterial infections of 94.0 and 59.8%,

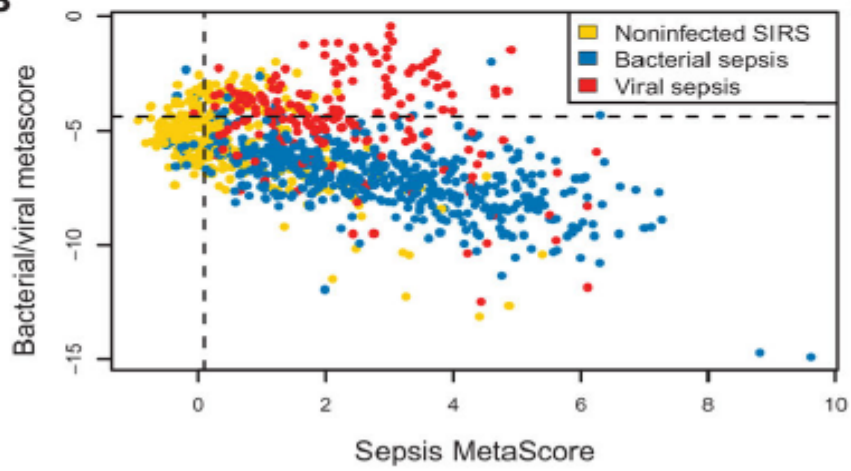
Sci Transl Med. 2016 July 06; 8(346): 346ra91.

Robust classification of bacterial and viral infections via integrated host gene expression diagnostics

Timothy E. Sweeney[1,2,*], Hector R. Wong[3,4], and Purvesh Khatri[1,2,*]



B

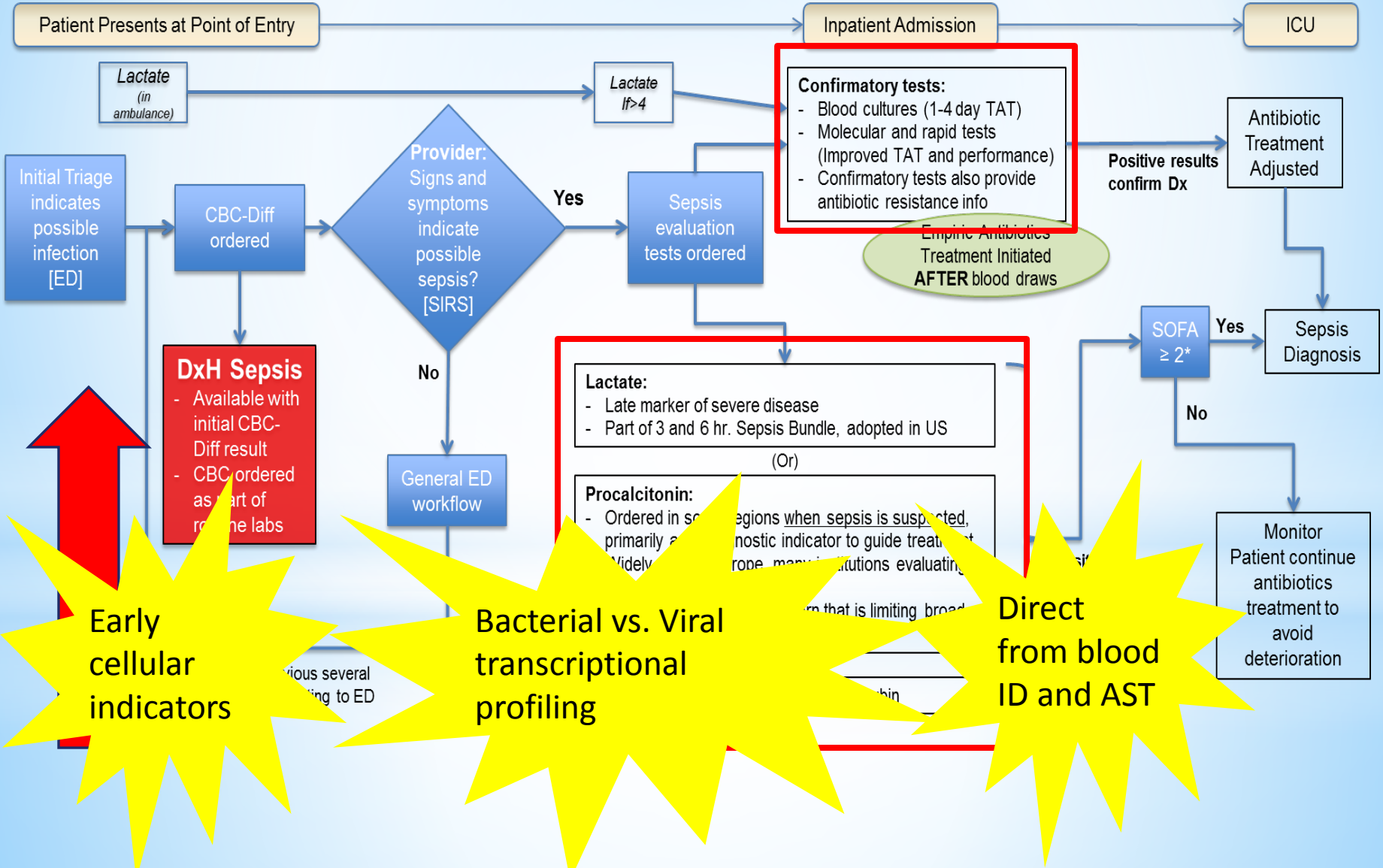


C

Ground truth	Predicted: Noninfected	Predicted: Bacterial	Predicted: Viral
Noninfected	137	115	67
Bacterial	19	504	13
Viral	1	94	107

Sci Transl Med. 2016 July 06; 8(346): 346ra91.

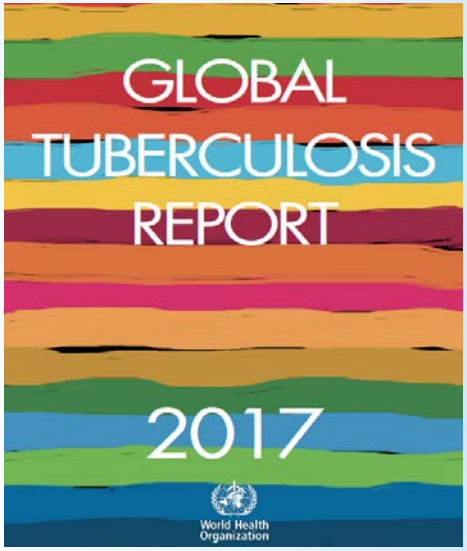
Diagnosing Sepsis BEFORE Blood Cultures are Drawn



Facts about Tuberculosis (TB)

Global burden of TB in 2016

- 10.4 million new cases
- 1.7 million died from TB
- est. 600,000 new cases with resistance to rifampicin
- 490,000 people with MDR-TB worldwide



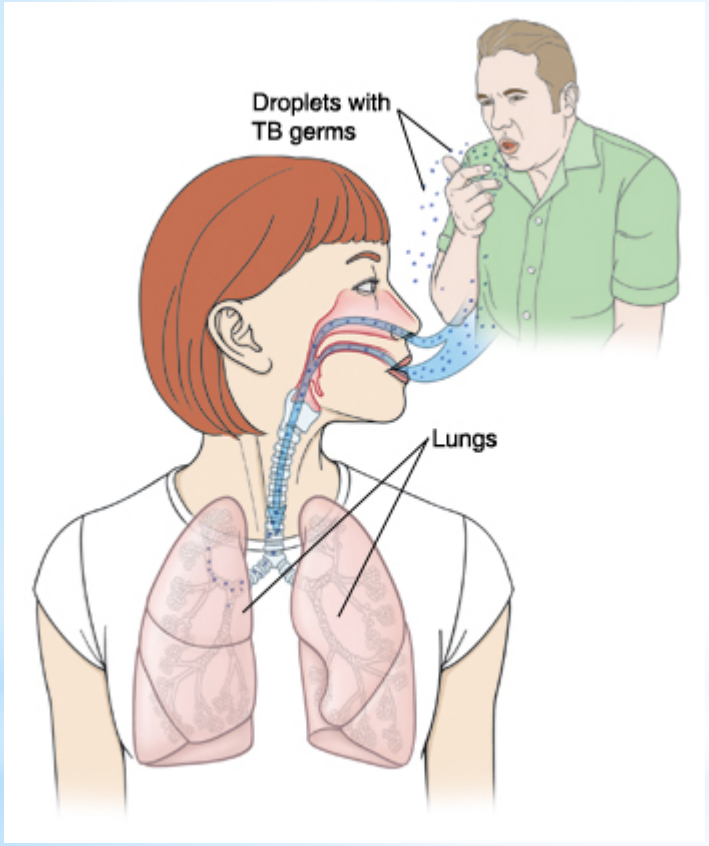
Fast access to test results is critical

- Accurate diagnosis
- Appropriate treatment
- Limit the spread of infection

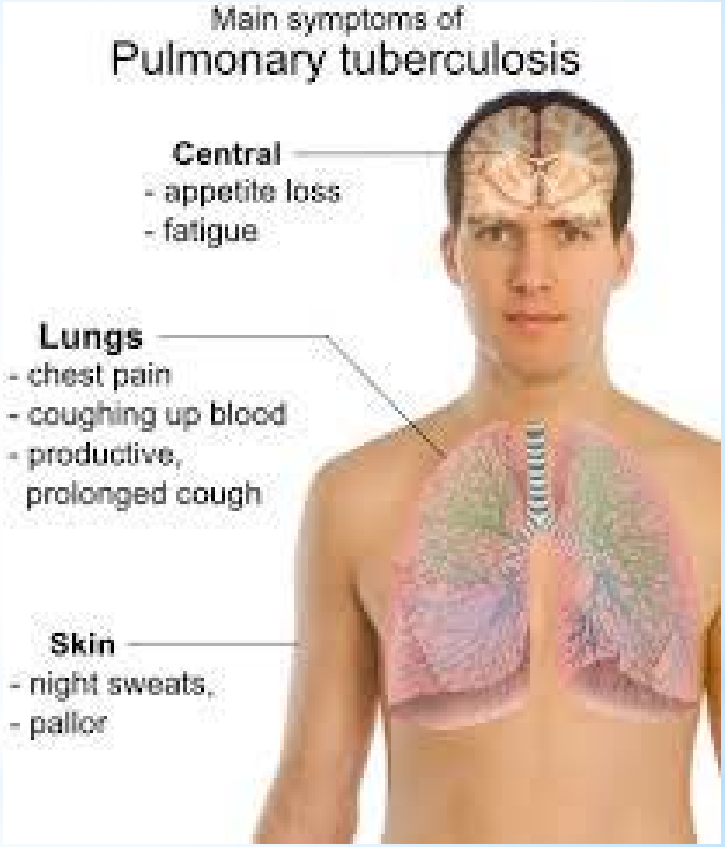
One third of new TB cases goes undiagnosed

Source:
1. Global Tuberculosis Report 20167 World Health Organization, http://www.who.int/tb/publications/global_report/gtbr2017_executive_summary.pdf?ua=1
2. Uplekar et al. WHO's new End TB strategy. Lancet. 2015 May 2;385(9979):1799-801.

Transmission and Symptoms of TB

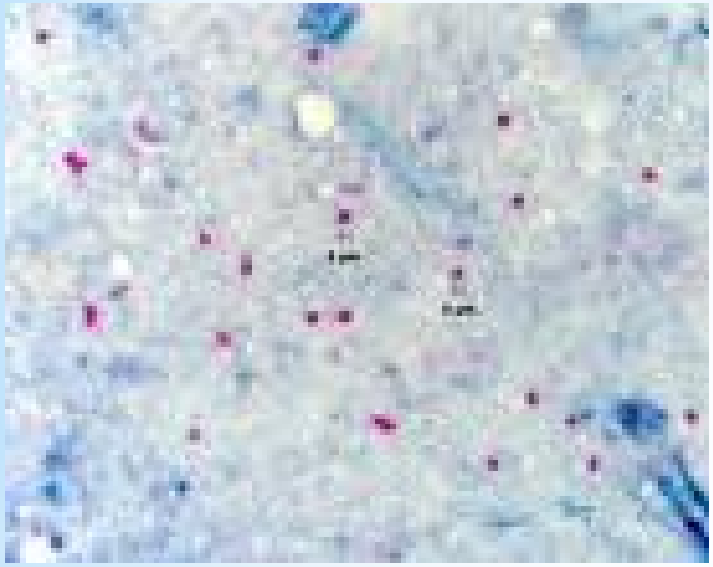


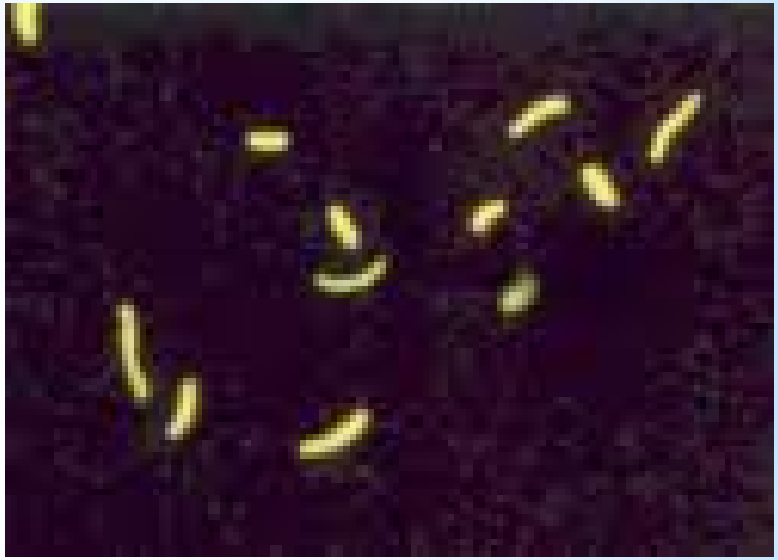
Droplets tend to hang in air from minutes to hours



TB may mimic several diseases, depending on presentation

Diagnostics: Acid Fast Smears – Ziehl-Neelsen and Auramine-Rhodamine





Red organisms on blue background

Organisms fluoresce yellow on black

Auramine-Rhodamine staining enhances sensitivity (10-20%)
Increases the number of microscopic fields that can be read quickly since a lower power of magnification can be used
Overall smear sensitivity 20-60%

Culture Systems for *Mycobacterium tuberculosis*

BD MGIT

BACTEC 9000

BACTI-Alert 3D

Liquid culture

Lowenstein-Jensen media

Agar culture

These semi-automated systems provide for continuously monitoring and reduce growth times from the 4-6 weeks time periods seen with solid media, like Lowenstein-Jensen agar, often to 1-2 weeks.

However, they are expensive, and contamination limits results.

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

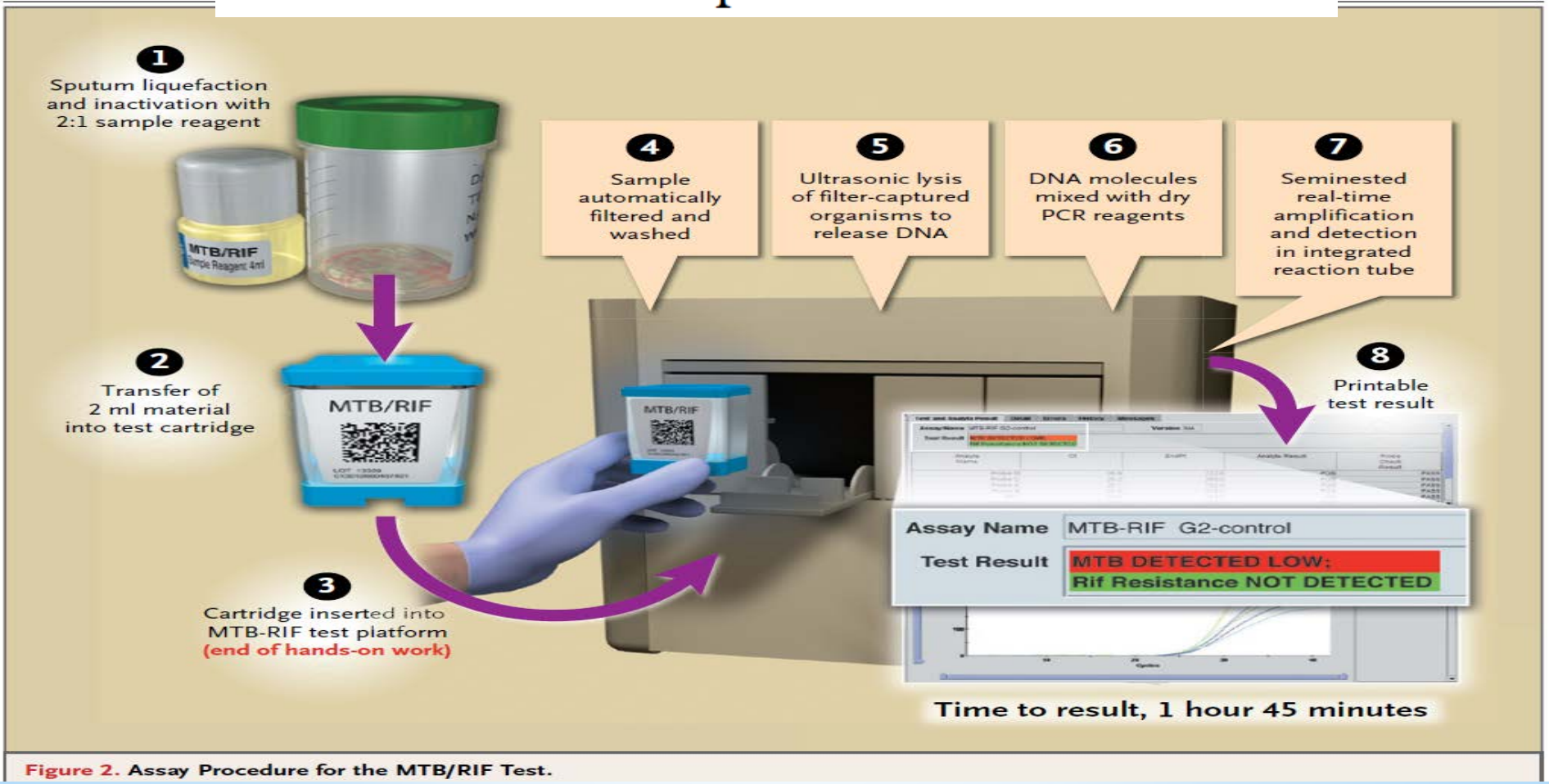


Figure 2. Assay Procedure for the MTB/RIF Test.

TB and rifampin resistance results in 1 hour 45 minutes direct from specimen

From: Boehme, *et.al.* NEJM 363:1005. Sept. 9, 2010

Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study

Lancet 2011; 377: 1495–1505

Catharina C Boehme, Mark P Nicol, Pamela Nabeta, Joy S Michael, Eduardo Gotuzzo, Rasim Tahirli, Ma Tarcela Gler, Robert Blakemore, William Worodria, Christen Gray, Laurence Huang, Tatiana Caceres, Rafail Mehdiyev, Lawrence Raymond, Andrew Whitelaw, Kalaiselvan Sagadevan, Heather Alexander, Heidi Albert, Frank Cobelens, Helen Cox, David Alland, Mark D Perkins

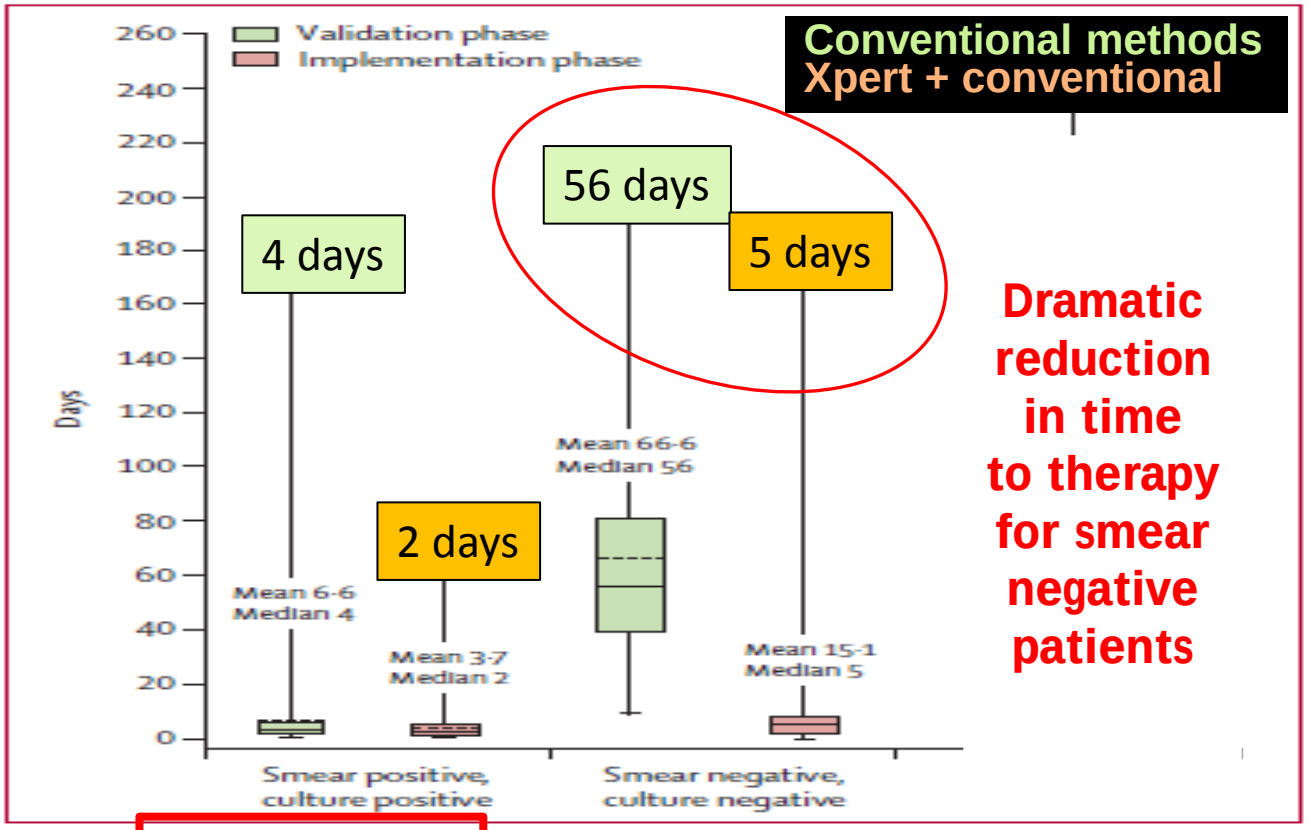


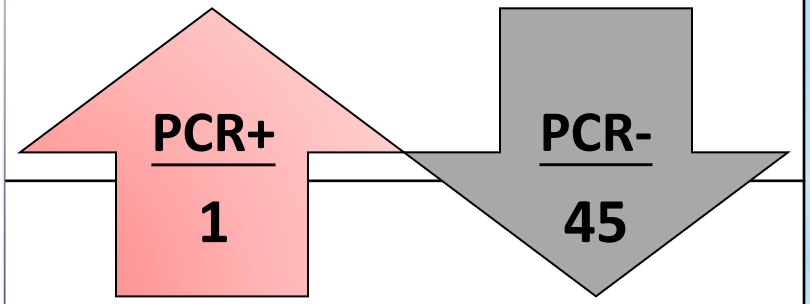
Figure 4: Time to treatment during validation phase (treatment based on conventional methods only) and implementation phase (treatment based on MTB/RIF test and conventional methods) for patients with smear-positive, culture-positive tuberculosis, smear-negative, culture-positive tuberculosis, or multidrug-resistant tuberculosis

Impact of GeneXpert MTB/RIF on Patients and Tuberculosis Programs in a Low-Burden Setting

A Hypothetical Trial

J. Lucian Davis[1,2], L. Masae Kawamura[3], Lelia H. Chaisson[1], Jennifer Grinsdale[3], Jihane Benhammou[4], Christine Ho[5], Anna Babst[6], Houmpheng Banouvong[3], John Z. Metcalfe[1,2], Mark Pandori[6], Philip C. Hopewell[1,2], and Adithya Cattamanchi[1,2]

Doctor judgment vs PCR	TB (n=13)	PCR shows its not TB (n=143)
Received empiric TB Rx		**47→3 Over-treatments** **Over-Rx Days: 2280→136**
No Empiric TB Rx		**96→140 Early rule-outs** Added Specificity = +31%



MTB Ultra Assay Performance vs. Xpert MTB/RIF Assay

	Xpert MTB/RIF Assay		MTB Ultra Assay	
	N	Percent (95% CI)	N	**Percent (95% CI)**
Sensitivity Smear Positives	342/344	99.4% (97.9, 99.8)	426/428	**99.5% (98.3, 99.9)**
Sensitivity Smear Negatives	128/222	57.7% (51.1, 64.0)	200/273	**73.3% (67.7, 78.2)**
Overall Sensitivity	474/570[a]	83.2% (79.9, 86.0)	630/705[a]	**89.4% (86.9, 91.4)**
Overall Specificity	1003/1024	97.9% (96.9, 98.7)	1222/1280	**95.5% (94.2, 96.5)**

[a]Smear result not available for 4 culture positive specimens.

CE-IVD. In vitro diagnostic medical device. Unpublished data

Clinical use of whole genome sequencing for *Mycobacterium tuberculosis*

Witney *et al. BMC Medicine* (2016) 14:46

Adam A. Witney[1*], Catherine A. Cosgrove[1,2], Amber Arnold[2], Jason Hinds[1], Neil G. Stoker[1] and Philip D. Butcher[1]

Genetic Mutations Associated with Isoniazid Resistance in *Mycobacterium tuberculosis*: A Systematic Review

PLOS ONE | DOI:10.1371/journal.pone.0119628 March 23, 2015

Marva Seifert, Donald Catanzaro, Antonino Catanzaro, Timothy C. Rodwell*

Table 4. Single and cumulative mutation frequencies on *katG*, *inhA*, and *ahpC-oxyR* among data subsets which assessed co-occurring mutations.

Gene Name (number of isolates)	Mutation type	Codon or Nucleotide Location	Resistant w/ Mutation	Cumulative Frequency (%)
katG (n = 6,134)	Single	315	4059	66.2
		309	36	0.6
		316	27	0.4
		311	27	0.4
	Cumulative	315, 309, 316, and/or 311	4068	66.3
inhA (n = 4,484)	Single	-15	854	19.0
		-8	46	1.0
		-47	15	0.3
		-17	11	0.2
	Cumulative	-15, -8, -47, and/or -17	926	20.6
ahpC-oxyR (n = 1,696)	Single	-10	20	1.2
		-6	25	1.5
		-39	13	0.8
		-48	3	0.2
		-15	13	0.8
		-12	9	0.5
		-9	8	0.5
	Cumulative	-10, -6, -39, -48, -15, -12, and/or -9	91	5.4
katG & *inhA* (n = 4,179)	Single	katG315	2723	65.2
		inhA -15	795	19.0
	Cumulative	katG315 and/or inhA -15	3337	79.9
katG & *inhA* & *ahpC-oxyR* (n = 1,582)	Single	katG315	1056	66.8
		inhA -15	257	16.2
	Cumulative	katG315 and/or inhA -15	1257	79.5
		katG315 and/or inhA -15, -8, -47, -17	1271	80.3
		katG315 and/or inhA -15, -8, -47, & -17 and/or ahpC -10, -6, -39, -48, -15, -12, & -9	1328	83.9

doi:10.1371/journal.pone.0119628.t004

The NEW ENGLAND JOURNAL of MEDICINE

Evaluation of a Rapid Molecular Drug-Susceptibility Test for Tuberculosis

Y.L. Xie, S. Chakravorty, D.T. Armstrong, S.L. Hall, L.E. Via, T. Song, X. Yuan, X. Mo, H. Zhu, P. Xu, Q. Gao, M. Lee, J. Lee, L.E. Smith, R.Y. Chen, J.S. Joh, Y.S. Cho, X. Liu, X. Ruan, L. Liang, N. Dharan, S.-N. Cho, C.E. Barry III, J.J. Ellner, S.E. Dorman, and D. Alland

Two hour test d1recty from sputum for 2nd line drug resistance detection in Xpert cartridge

Table 2. Sensitivity and Specificity of the Investigational Assay, with Phenotypic Drug-Susceptibility Testing as the Reference Standard, in the Main Analysis Population for Drug-Susceptibility Testing.

Drug	Investigational-Assay Result + Phenotypic Drug-Susceptibility Test Result*				Sensitivity		Specificity	
	R+R	R+S	S+R	S+S				
	no. of specimens				*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Isoniazid†	150	1	30	122	150/180	83.3 (77.1–88.5)	122/123	99.2 (95.6–100.0)
Ofloxacin‡	84	7	11	201	84/95	88.4 (80.2–94.1)	201/208	96.6 (93.2–98.6)
Moxifloxacin, 0.5 μg/ml‡§	78	12	11	200	78/89	87.6 (79.0–93.7)	200/212	94.3 (90.3–97.0)
Moxifloxacin, 2.0 μg/ml‡	51	40	2	210	51/53	96.2 (87.0–99.5)	210/250	84.0 (78.9–88.3)
Kanamycin¶	35	4	14	245	35/49	71.4 (56.7–83.4)	245/249	98.4 (96.0–99.6)
Amikacin¶	29	1	12	256	29/41	70.7 (54.5–83.9)	256/257	99.6 (97.9–100.0)

N Engl J Med 2017;377:1043-54.

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Problems with phenotypic drug susceptibility testing becoming apparent

Table 3. Sensitivity and Specificity of the Investigational Assay, with DNA Sequencing as the Reference Standard, in the Main Analysis Population for Drug-Susceptibility Testing.*

Drug	Investigational-Assay Result + DNA Sequencing Result†				Sensitivity		Specificity	
	M+M	M+NM	NM+M	NM+NM				
	no. of specimens				*no./total no.*	*% (95% CI)*	*no./total no.*	*% (95% CI)*
Isoniazid‡	151	0	3	149	151/154	98.1 (94.4–99.6)	149/149	100.0 (97.6–100.0)
Fluoroquinolones§	91	0	4	208	91/95	95.8 (89.6–98.8)	208/208	100.0 (98.2–100.0)
Kanamycin¶	38	1	3	256	38/41	92.7 (80.1–98.5)	256/257	99.6 (97.9–100.0)
Amikacin¶	30	0	1	267	30/31	96.8 (83.3–99.9)	267/267	100.0 (98.6–100.0)

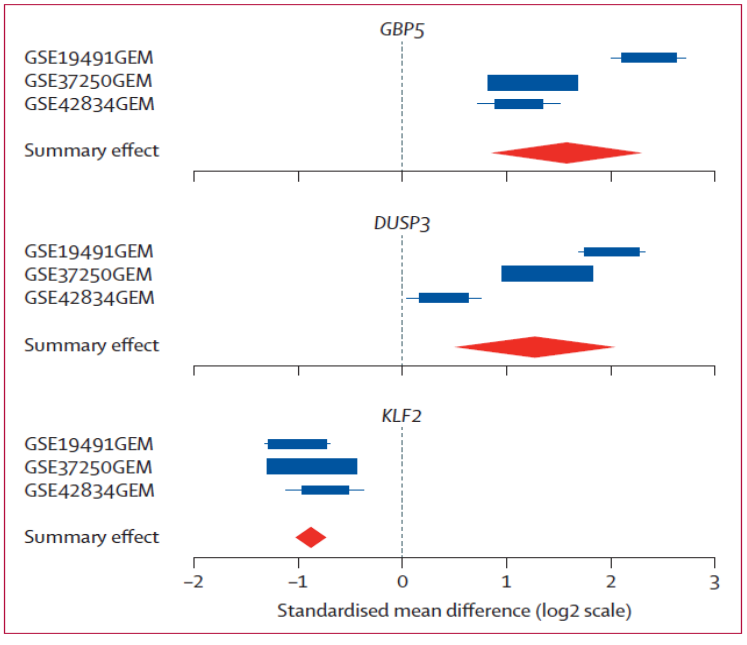
N Engl J Med 2017;377:1043-54.

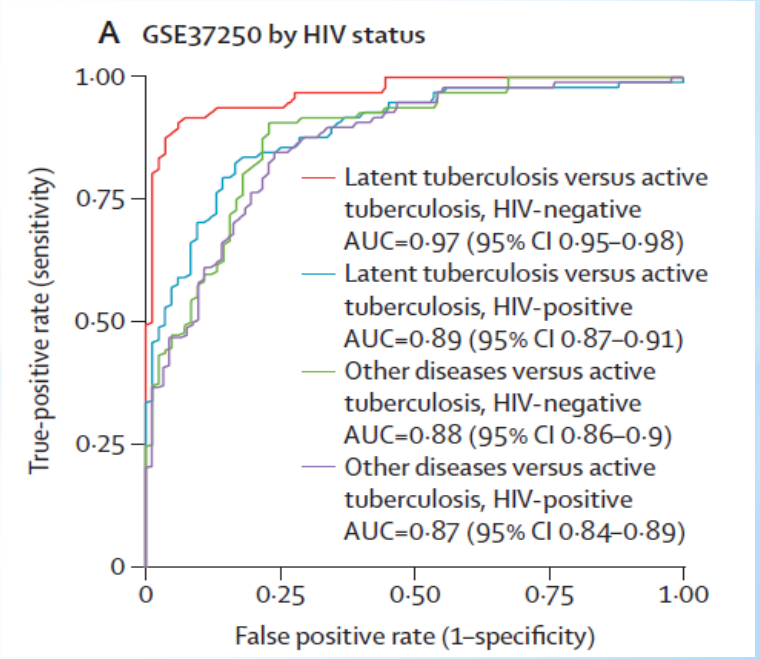
Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis

Lancet Respir Med 2016; 4: 213–224

Timothy E Sweeney, Lindsay Braviak, Cristina M Tato, Purvesh Khatri

- **What about patients that don't produce sputum or are difficult to diagnose?**
- **Looked for markers in whole blood from14 large data sets, 2572 samples from 10 countries, included adult and pediatric patients**
- **Identified 266 candidate genes (158 over-expressed; 108 under-expressed)**
- **Narrowed down to 3 genes**
- **Could be done on 100µ L of blood from a finger-stick**





Testing for Chlamydia and Gonorrhea at a London Sexually Transmitted Disease Clinic

In the heart of London's popular Soho

Asymptomatic STI screening

Results within hours

Nurse-led Service

An early evaluation of clinical and economic costs and benefits of implementing point of care NAAT tests for *Chlamydia trachomatis* and *Neisseria gonorrhoea* in genitourinary medicine clinics in England

Sex Transm Infect 2013;**0**:1–8.

Katherine M E Turner,[1] Jeff Round,[2] Patrick Horner,[1] John Macleod,[1] Simon Goldenberg,[3] Arminder Deol,[4] Elisabeth J Adams[1,4]

- In this model, using Xpert CT/NG as a POCT for same day diagnosis would save an estimated $19 million annually (economic impact)
- Would prevent 95,000 unnecessary treatments per year (stewardship)
- Would prevent 17,561 transmissions of disease annually (public health)
- Would significantly reduce patient anxiety for those getting negative results the same day versus 10 days (Patient impact)
- In reality, results exceeded expectation. Testing volume increased from 10,000 specimens/year to >200,0000/year

Original research article

Gary G Whitlock[1], Daniel C Gibbons[2,3], Nick Longford[4], Michael J Harvey[2], Alan McOwan[1] and Elisabeth J Adams[2,5]

INTERNATIONAL JOURNAL OF STD & AIDS

Rapid testing and treatment for sexually transmitted infections improve patient care and yield public health benefits

International Journal of STD & AIDS
0(0) 1–9

DOI: 10.1177/0956462417736431
journals.sagepub.com/home/std
SAGE

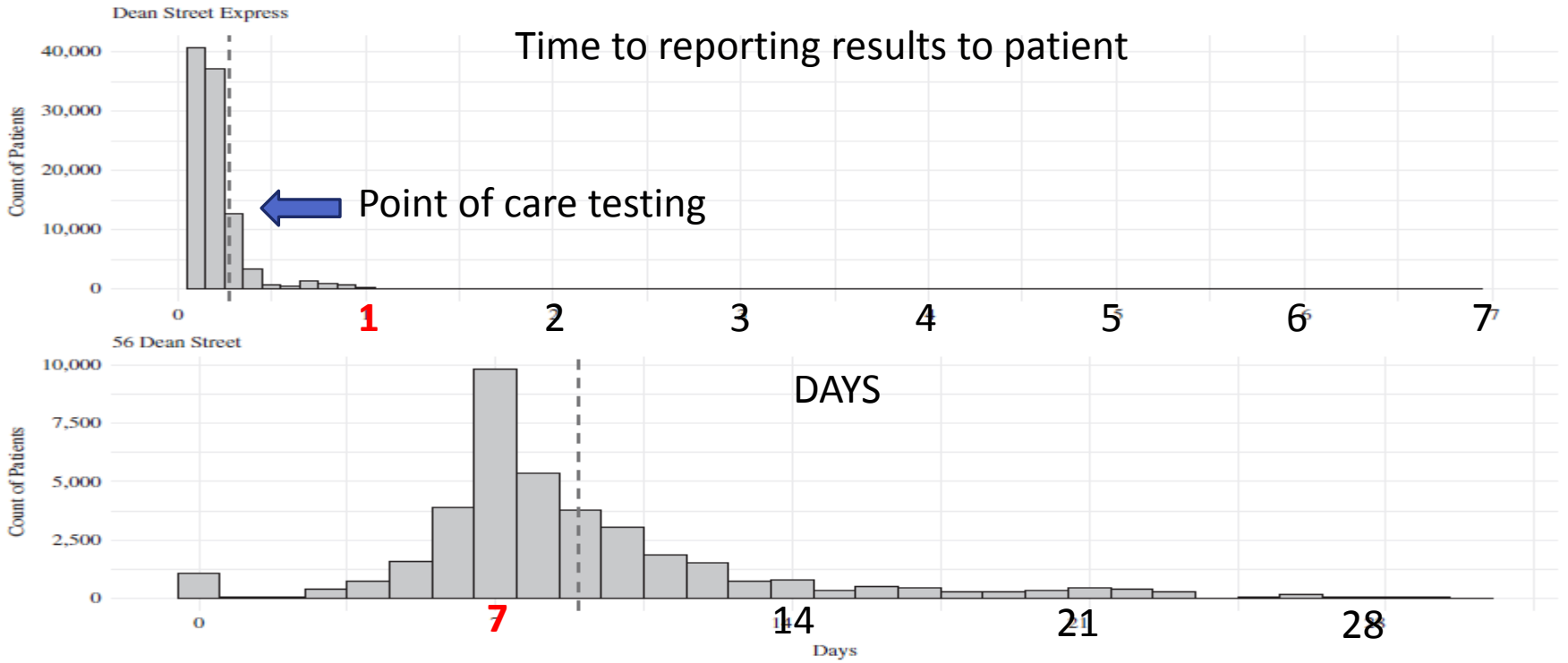


Figure 2. Time from testing visit to results being reported to patients by text message; for Dean Street Express and 56 Dean Street. Broken vertical lines denote the mean.

A Randomized Controlled Trial Comparing the Treatment of Patients Tested for Chlamydia and Gonorrhea After a Rapid Polymerase Chain Reaction Test Versus Standard of Care Testing

Larissa May, MD, Chelsea E. Ware, MS,† Jeanne A. Jordan, PhD,† Mark Zocchi, MPH,‡§ Catherine Zatorski, BA,† Yasser Ajabnoor, MD,† and Jesse M. Pines, MD‡§*

Used PCR test in Emergency Department at George Washington University Medical Center, Washington, D.C.

TABLE 2. Results: Study Patients Versus Controls

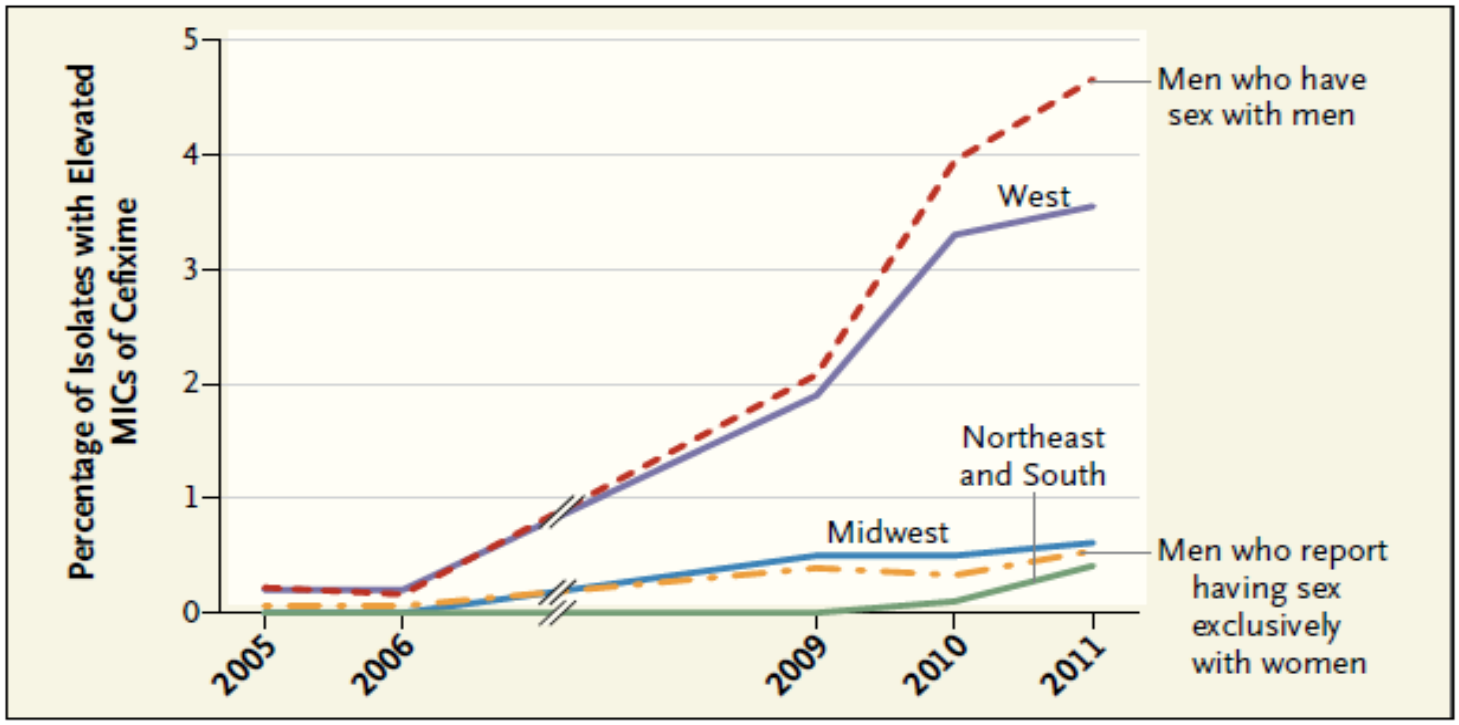
Outcome Measures	Test	Control	Difference, %	95% CI	RR	95% CI
All Patients (N = 70)	n = 42	n = 28				
Empiric treatment for CTNG	12 (28.6)	17 (60.7)	−32.1	−54.8 to −9.5	0.47	0.27–0.83
Mean total charges (SD)	US $2503 (923)	US $3058 (1716)	−US $555	−US $155 to US $1264		
With negative test results (N = 57)	n = 37	n = 20				
Empiric treatment for CTNG	8 (21.6)	11 (55.0)	−33.4	−58.9 to −7.9	0.39	0.19–0.82

Results: Significant reduction in empiric antibiotic therapy using rapid diagnostic test with no negative impact to patient care

NEJM Perspective
FEBRUARY 9, 2012

The Emerging Threat of Untreatable Gonococcal Infection

Gail A. Bolan, M.D., P. Frederick Sparling, M.D., and Judith N. Wasserheit, M.D., M.P.H.



Percentage of Isolates in Which Minimal Inhibitory Concentrations (MICs) of Cefixime Were 0.25 μg per Milliliter or Higher, 2005–2011.

Gonococcal isolates with multidrug resistant phenotypes rising globally

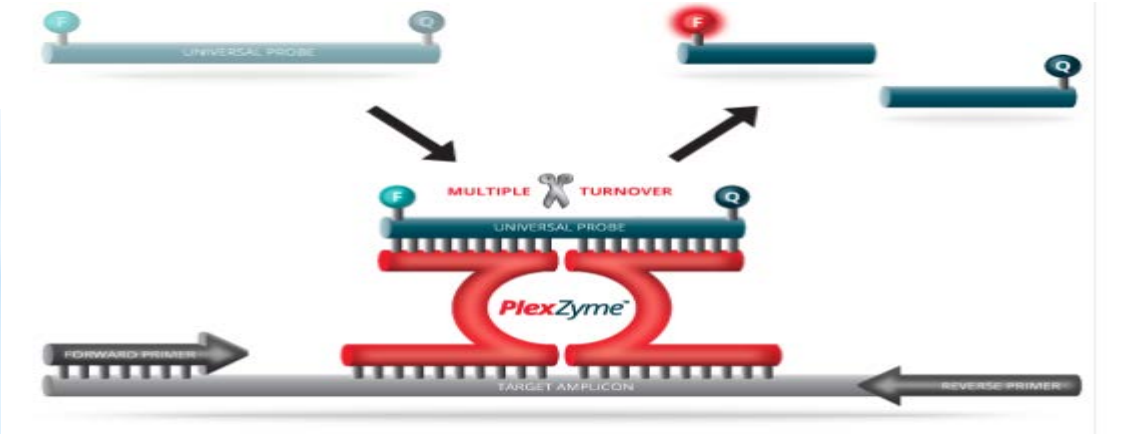
Sometimes Pathogen Identification Isn't Enough: *Mycoplasma genitalium*

*Resistance*Plus™ MG

Resistance*Plus*™ MG Specifications Resources Ordering

Resistance*Plus*™ MG is a multiplex qPCR test for detection of *Mycoplasma genitalium* and five macrolide resistance markers from male and female urine and swab specimens. Proprietary ***Plex****Zyme*™ and ***Plex****Prime*™ technologies improve multiplex performance compared with other probe-based tests allowing for multiple mutation detection in a single well.

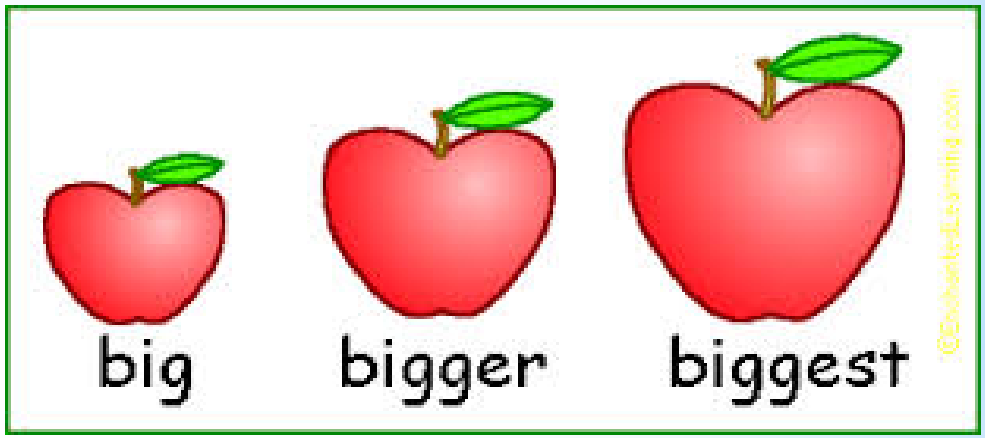
CE IVD



>40% of *M. genitalium* strains are resistant to azithromycin, the drug of choice

What Has Changes in Rapid Diagnostics in the Last Few Years?

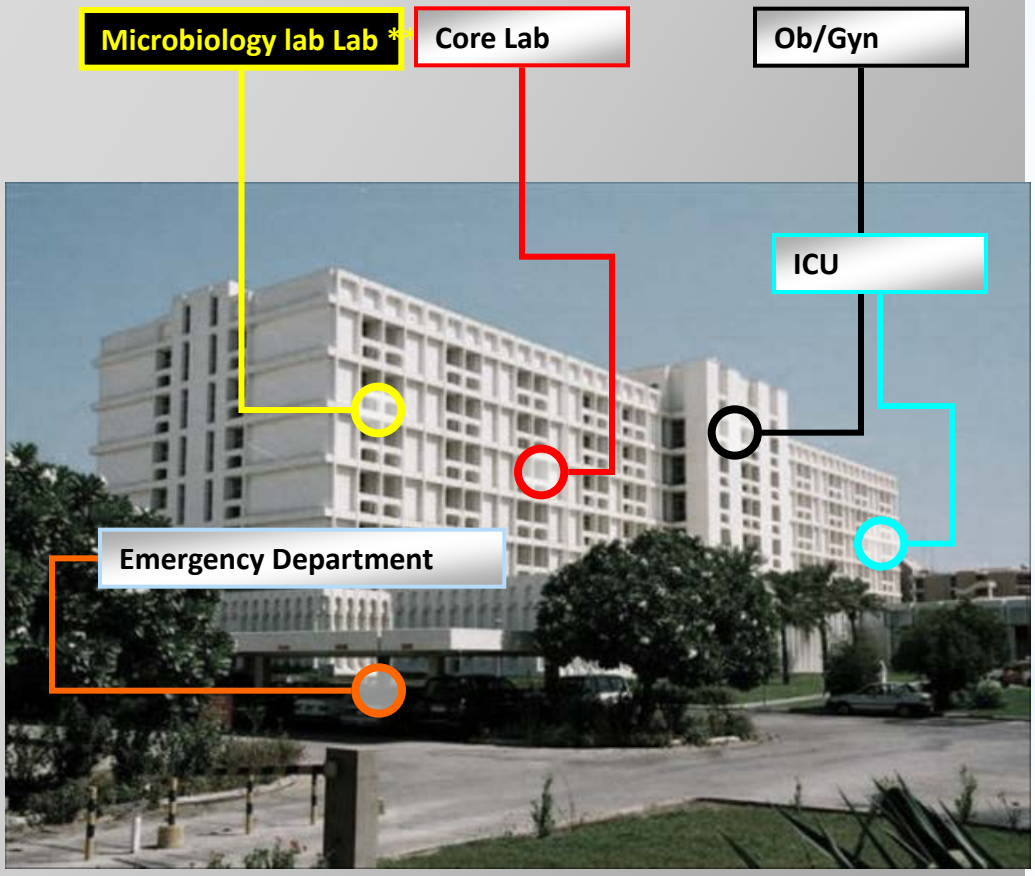
Faster time to result for single assays e.g., influenza



More targets for blood, respiratory, gastrointestinal and meningitis/encephalitis panels

Moderately Complex Diagnostic Tests Can be Performed Almost Anywhere

Within the hospital



**Micro lab provides oversight for quality assurance

Beyond the hospital

- Satellite/Reference Labs
- Outpatient Clinics
- Surgery Centers
- Urgent Care
- POC molecular CLIA-waived tests are now available

A New Generation of Rapid, Point of Care Diagnostic Platforms

GeneXpert®
Xpress Flu

FDA Cleared

cobas Liat
Lab in a tube

FDA Cleared

Alere™ i Influenza A & B

FDA Cleared

New Notions of Point of Care Testing

Use of POC molecular diagnostics for tuberculosis, HIV, and sexually transmitted infections are impacting medical care

Sexual health clinics

In patient testing

Clinical Microbiology and Infection 23 (2017) 2–22

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Review

The role of whole genome sequencing in antimicrobial susceptibility testing of bacteria: report from the EUCAST Subcommittee

M.J. Ellington [1, †], O. Ekelund [2, †], F.M. Aarestrup [3], R. Canton [4], M. Doumith [1], C. Giske [5], H. Grundman [6], H. Hasman [7], M.T.G. Holden [8], K.L. Hopkins [1], J. Iredell [9], G. Kahlmeter [2], C.U. Köser [10], A. MacGowan [11], D. Mevius [12, 13], M. Mulvey [14], T. Naas [15], T. Peto [16], J.-M. Rolain [17], Ø. Samuelsen [18], N. Woodford [1, *]

The published evidence for using WGS as a tool to infer antimicrobial susceptibility accurately is currently either poor or non-existent and the evidence / knowledge base requires significant expansion.

Better Tests, Better Care: Improved Diagnostics for Infectious Diseases

Clinical Infectious Diseases 2013;57(S3):S139–70

Angela M. Caliendo,[1] David N. Gilbert,[2,3] Christine C. Ginocchio,[4,5,6] Kimberly E. Hanson,[7,8] Larissa May,[9] Thomas C. Quinn,[10,11] Fred C. Tenover,[12] David Alland,[13] Anne J. Blaschke,[14] Robert A. Bonomo,[15,16,17,18] Karen C. Carroll,[19,20] Mary Jane Ferraro,[21,22] Lisa R. Hirschhorn,[23,24] W. Patrick Joseph,[25,26,27,28] Tobi Karchmer,[29] Ann T. MacIntyre,[30,31] L. Barth Reller,[32,33] and Audrey F. Jackson;[34] for the Infectious Diseases Society of America (IDSA)

Educate Healthcare Providers on the Use of Diagnostics

2. Professional societies, educational institutions, and other entities involved in the education of clinicians, including graduate medical education, continuing medical education, and maintenance of certification, should ensure that education includes the performance of diagnostic tests, interpretation of test results in individual clinical settings with varied patient populations, available guidelines, and cost of testing.

Expedite Integration of Improved Diagnostic Tests Into Patient Care

3. Outcomes research should be supported that addresses the need for data on diagnostics use in varied clinical settings and data to document the effect of diagnostic testing on the individual patient and the healthcare system.

*Final Thoughts

- We are clearly in the era of molecular diagnostics, where the focus is on rapid pathogen identification
- This includes molecular diagnostics for sepsis, tuberculosis, sexually transmitted infections, gastrointestinal diseases and other infections
- The next wave of diagnostics will be focused on host response markers to answer the question of whether or not an infection is present
- Many exciting new technologies are impacting healthcare in positive ways


THANK YOU
FOR YOUR
ATTENTION