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.
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

- **Gram-positive, Gram-negative bacteria**
  1. Minimize passage numbers
  2. Select colony
  3. Spot target organism, overlay with 1 mL Formic Acid
  4. Full extraction with Ethanol and Formic Acid

- **Non-fermenting Gram-negative bacteria**
  1. Minimize passage numbers
  2. Select colony
  3. Spot target organism (optional Formic Acid overlay)

- **Anaerobic bacteria**
  1. Minimize passage numbers
  2. Select colony
  3. Spot target organism, overlay with 1 mL Formic Acid

- **Mycobacteria**
  1. Transfer bacteria to screw cap tube containing water and detergent (Tween)
  2. Heat at 95°C for 1 hour to inactivate bacteria
  3. Add Formic Acid/Acetonitrile mixture

- **Nocardia, Actinomycetes**
  1. Boil large amounts of bacteria (turbid suspension)
  2. Ethanol extraction, dry pellets, and resuspend in Formic Acid

- **Yeast**
  1. Culture 24 to 72 hours depending upon fungal species and media type
  2. Select colony
  3. Spot target organism, overlay with 1 mL Formic Acid
  4. Full extraction with Ethanol and Formic Acid/Acetonitrile

Add matrix to sample and analyze.
Need to Change the Slow Delivery of Results With Low Medical Impact

- Specimen Taken
- Culture
- Prelim report
- Susceptibility test
- Susceptibility test (fastidious)
- Mixed infections report to doctor

Hours:
- 24
- 48
- 72
- 96 (4 days!!!)

Medical Value
Molecular Methods Change the Paradigm

Specimen Taken/Positive Blood Culture

PCR report

Medical Value

Final report to doctor for mixed infection

Susceptibility test (fastidious)

Susceptibility test

Culture

PCR testing

Optimal antimicrobial therapy initiated

Hours

0 1-3 24
Examples of Molecular Diagnostics for Blood Cultures: *S. aureus*, MRSA, Coagulase Negative Staphylococci

Gram + cocci  in clusters

- **MALDI-TOF ID**
- **PCR/Array with nanopropbes: Nanosphere (3 hours)**
- **Filmarray (BioFire): S. aureus, mecA resistance genes (1 hour)**
- **PCR testing Xpert MRSA/SA (~1 hour)**

All these methods provide bacterial identifications in 1-3 hours, so targeted therapy can be started.
Getting patients on the right drug 10 times faster or off the wrong drugs 4 times faster improves outcomes.
1 Test. 27 Targets. All in about an hour.

**Gram + Bacteria**
- Enterococcus
- Listeria monocytogenes
- Staphylococcus
- Staphylococcus aureus

**Gram – Bacteria**
- Acinetobacter baumannii
- Haemophilus influenzae
- Neisseria meningitidis
- Pseudomonas aeruginosa

**Yeast**
- Candida albicans
- Candida glabrata
- Candida krusei
- Candida parapsilosis
- Candida tropicalis

**Antibiotic Resistance**
- **mecA** - methicillin resistant
- **vanA/B** - vancomycin resistant
- **KPC** - carbapenem resistant
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

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

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

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. Pappas12

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

A

~2 ml blood sample → Blood cell lysis & Candida cell concentration → Remove supernatant → Lyse Candida cells → PCR lysate → Aliquot & hybridize with particles → T2 detection

B

Target complementary capture probe A

Target complementary capture probe B

Add sample (i.e., blood containing target DNA)

DNA target hybridizes to capture probes forming interparticle linkages. A change in T2 is measured as agglomeration ensues.
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

Patient Presents at Point of Entry

- Lactate (in ambulance)
  - Lactate if >4

Provider: Signs and symptoms indicate possible sepsis? [SIRS]

- CBC-Diff ordered
  - If positive, SIRS criteria met

DxH Sepsis
- Available with initial CBC-Diff result
- CBC ordered as part of routine labs

No

Yes

Sepsis evaluation tests ordered

- Blood cultures (1-4 day TAT)
- Molecular and rapid tests (improved TAT and performance)
- Confirmatory tests also provide antibiotic resistance info

Empirical Antibiotics Treatment Initiated AFTER blood draws

Inpatient Admission

- Positive results confirm Dx
  - Antibiotic Treatment Adjusted

ICU

General ED workflow

Lactate:
- Late marker of severe disease
- Part of 3 and 6 hr. Sepsis Bundle, adopted in US

(Or)

Procalcitonin:
- Ordered in some regions when sepsis is suspected, primarily as a prognostic indicator to guide treatment
- Widely used in Europe, many institutions evaluating and using selectively in US
- VOC: cost/benefit is a concern that is limiting broad adoption in the US

(And/or)

Other tests: C-reactive Protein, IL6, Bilirubin

Symptoms obvious several hours after presenting to ED

Positive results

Sepsis Diagnosis

Monitor Patient continue antibiotics treatment to avoid deterioration
Sepsis

- 5 million cases per year worldwide and growing
- Highly morbid (> 30%) and 10th leading cause of death in US; 12.6% of deaths in hospital
- Each hour delay of effective antibiotics increases mortality

Current Diagnostic Landscape

- Many different modalities used to diagnose and monitor sepsis today
- >90% of doctors want to increase confidence in sepsis diagnosis and want IT systems to speed up diagnosis

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

Innovation: Sepsis Opportunity

Opportunity to reduce highest healthcare costs by earlier diagnosis of 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\(^2\)
* \(\Delta\) neutrophil volume distribution width (variation in size) is an early sign of bacterial infection\(^3\)

MDW = 19.1  
WBC cells x10³ = 4.73

MDW = 24.3  
WBC cells x10³ = 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. Sweeney¹,²,* Hector R. Wong³,⁴, and Purvesh Khatri¹,²,*

Validation whole blood, COCONUT-cononormalized global AUC = 0.93 (95% CI 0.91–0.94)

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%,

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

Timothy E. Sweeney\textsuperscript{1,2,*}, Hector R. Wong\textsuperscript{3,4}, and Purvesh Khatri\textsuperscript{1,2,*}

Diagnosing Sepsis BEFORE Blood Cultures are Drawn

Initial Triage indicates possible infection [ED]

Lactate (in ambulance)

Patient Presents at Point of Entry

Lactate if >4

CBC-Diff ordered

Provider: Signs and symptoms indicate possible sepsis? [SIRS]

Yes

Sepsis evaluation tests ordered

Positive results confirm Dx

Empiric Antibiotics Treatment Initiated AFTER blood draws

Direct from blood ID and AST

Lactate:
- Late marker of severe disease
- Part of 3 and 6 hr. Sepsis Bundle, adopted in US

Procalcitonin:
- Ordered in some regions when sepsis is suspected, primarily as a prognostic indicator to guide treatment
- Widely used in Europe, many institutions evaluating role in diagnosis

Bacterial vs. Viral transcriptional profiling

Early cellular indicators

Inpatient Admission

ICU

Sepsis Diagnosis

Monitor Patient continue antibiotics treatment to avoid deterioration

No

General ED workflow

SOFa ≥ 2*

Yes

Antibiotic Treatment Adjusted

No

DxH Sepsis
- Available with initial CBC-Diff result
- CBC ordered as part of routine labs

Initial ED triage referring to ED

Previous several times referring to ED

Confirmed several times referring to ED

Confidential several times referring to ED
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

Source:
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*

<table>
<thead>
<tr>
<th>Liquid culture</th>
<th>Agar culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD MGIT</td>
<td>Lowenstein-Jensen media</td>
</tr>
<tr>
<td>BACTEC 9000</td>
<td></td>
</tr>
<tr>
<td>BACTI-Alert 3D</td>
<td></td>
</tr>
</tbody>
</table>

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

1. Sputum liquefaction and inactivation with 2:1 sample reagent
2. Transfer of 2 ml material into test cartridge
3. Cartridge inserted into MTB-RIF test platform (end of hands-on work)
4. Sample automatically filtered and washed
5. Ultrasonic lysis of filter-captured organisms to release DNA
6. DNA molecules mixed with dry PCR reagents
7. Seminested real-time amplification and detection in integrated reaction tube

Time to result, 1 hour 45 minutes

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

Catharina C Boehme, Mark P Nicol, Pamela Nabeta, Joy S Michael, Eduardo Gotuzzo, Rasim Tahirî, Ma Teresa 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
## Doctor judgment vs PCR

<table>
<thead>
<tr>
<th></th>
<th>TB (n=13)</th>
<th>PCR shows its not TB (n=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received empiric TB Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Empiric TB Rx</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Over-treatments**: 47 → 3
- **Over-Rx Days**: 2280 → 136
- **Early rule-outs**: 96 → 140
- **Added Specificity**: +31%

**Diagram:**
- PCR+ 1
- PCR- 45
### MTB Ultra Assay Performance vs. Xpert MTB/RIF Assay

<table>
<thead>
<tr>
<th></th>
<th>Xpert MTB/RIF Assay</th>
<th>MTB Ultra Assay</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Percent (95% CI)</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear Positives</td>
<td>342/344</td>
<td>99.4% (97.9, 99.8)</td>
</tr>
<tr>
<td>Smear Negatives</td>
<td>128/222</td>
<td>57.7% (51.1, 64.0)</td>
</tr>
<tr>
<td>Overall Sensitivity</td>
<td>474/570(^a)</td>
<td>83.2% (79.9, 86.0)</td>
</tr>
<tr>
<td>Overall Specificity</td>
<td>1003/1024</td>
<td>97.9% (96.9, 98.7)</td>
</tr>
</tbody>
</table>

\(^a\)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*

Adam A. Witney, Catherine A. Cosgrove, Amber Arnold, Jason Hinds, Neil G. Stoker and Philip D. Butcher

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

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

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

<table>
<thead>
<tr>
<th>Gene Name (number of isolates)</th>
<th>Mutation type</th>
<th>Codon or Nucleotide Location</th>
<th>Resistant Mutation</th>
<th>Cumulative Frequency (%)</th>
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</thead>
<tbody>
<tr>
<td><em>katG</em> (n = 6,134)</td>
<td>Single</td>
<td>315</td>
<td>4059</td>
<td>66.2</td>
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<tr>
<td></td>
<td></td>
<td>309</td>
<td>36</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>316</td>
<td>27</td>
<td>0.4</td>
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<td></td>
<td></td>
<td>311</td>
<td>27</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Cumulative</td>
<td>315, 309, 316, and/or 311</td>
<td>4068</td>
<td>66.3</td>
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<tr>
<td></td>
<td></td>
<td>-15</td>
<td>854</td>
<td>19.0</td>
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<tr>
<td></td>
<td></td>
<td>-8</td>
<td>46</td>
<td>1.0</td>
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<td></td>
<td></td>
<td>-47</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-17</td>
<td>11</td>
<td>0.2</td>
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<td>Cumulative</td>
<td>-15, -8, -47, and/or -17</td>
<td>926</td>
<td>20.6</td>
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<td>1.2</td>
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<td>0.8</td>
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<td>0.2</td>
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<td>0.8</td>
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<td>-12</td>
<td>9</td>
<td>0.5</td>
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<tr>
<td></td>
<td></td>
<td>-9</td>
<td>8</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Cumulative</td>
<td>-10, -6, -39, -48, -15, -12, and/or -9</td>
<td>91</td>
<td>5.4</td>
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<tr>
<td></td>
<td><em>katG</em></td>
<td>-15</td>
<td>2723</td>
<td>65.2</td>
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<td></td>
<td><em>katG</em></td>
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<td>795</td>
<td>19.0</td>
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<tr>
<td></td>
<td>Cumulative</td>
<td><em>katG</em>315 and/or <em>inhA</em>-15</td>
<td>3337</td>
<td>79.9</td>
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<tr>
<td></td>
<td><em>katG</em></td>
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<td>257</td>
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<td>Cumulative</td>
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<td>1257</td>
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<td></td>
<td><em>katG</em></td>
<td>-15</td>
<td>1328</td>
<td>83.9</td>
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dd:10.1371/journal.pone.0119628.s004

PLOS ONE | DOI:10.1371/journal.pone.0119628 | March 23, 2015
Two hour test directly from sputum for 2nd line drug resistance detection in Xpert cartridge
Problems with phenotypic drug susceptibility testing becoming apparent
What about patients that don’t produce sputum or are difficult to diagnose?
- Looked for markers in whole blood from 14 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 100µL 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
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 >200,000/year.
Rapid testing and treatment for sexually transmitted infections improve patient care and yield public health benefits

Time to reporting results to patient

Point of care testing

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.
Results: Significant reduction in empiric antibiotic therapy using rapid diagnostic test with no negative impact to patient care.
Gonococcal isolates with multidrug resistant phenotypes rising globally
Sometimes Pathogen Identification Isn’t Enough: *Mycoplasma genitalium*

*ResistancePlus™ MG*

*ResistancePlus™ 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 PlexZyme™ and PlexPrime™ technologies improve multiplex performance compared with other probe-based tests allowing for multiple mutation detection in a single well.

>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
- Microbiology lab Lab *
- Core Lab
- Ob/Gyn
- ICU
- Emergency Department

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

**Micro lab provides oversight for quality assurance**
A New Generation of Rapid, Point of Care Diagnostic Platforms

GeneXpert® Xpress Flu

cobas Liat

Alere™ i Influenza A & B

FDA Cleared FDA Cleared 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.
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.
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