Update in Infectious Diseases
Part 1: Diagnostic Test Utilization
in the Era of Syndromic Molecular Panels

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Disclosures

- Research Support
  - Merck and Co
  - Nanosphere
  - Biofire
  - Immunexpress
  - OpGen
  - Theravance

- Speaker’s Fees
  - Nanosphere
  - OpGen
Objectives

- Understand the importance of diagnostic utilization
- Understand opportunities to improve test utilization
- Understand appropriate use of and emerging issues related to multiplex molecular tests used for respiratory infections
“Medicine is a science of uncertainty and an art of probability”

Sir William Osler
General Approach to Patients with Infectious Diseases

**Diagnosis/disease**
(eg. Meningitis)

↓

**Most likely organism**

↓

**Best OR NO Antimicrobial**

**Bayesian Reasoning**

Consider:

a. History
b. Physical exam
c. Lab studies/cultures
Bayes Theorem

- Probability of an event based on prior knowledge of conditions that might be related to the event
- How to revise our beliefs in the light of evidence
- Important considerations:
  - Tests are not the event
  - Tests are flawed
Revolution in Clinical Microbiology: Rapid Molecular Diagnostics

**Approved Indications:**
- MRSA
- *C. difficile*
- GAS
- GBS
- Norovirus
- Tuberculosis
- Bloodstream Infection
- Respiratory Tract Infection
- Gastroenteritis
- Meningitis

**Pipeline:**
- Pneumonia
- Joint Infections

*NOT FREE*
Benefits of Rapid Diagnostic Tests

- Improved laboratory workflow (ie. Faster TAT)
- Improved antibiotic use
- Decrease length of stay
- Decrease mortality
- Decrease cost of care
- Prevent spread of communicable diseases
Technology is great, until it isn’t
# Rates of Inappropriate Testing: 1997-2012

Ming Zhi, and others. PLOS ONE, Nov 2013. 8(11)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Error rate (95% CI)</th>
<th>Difference (95% CI)</th>
<th>n</th>
<th>Stratum differences</th>
<th>Variability explained</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Overutilization</td>
<td>20.6 (16.2, 24.9)</td>
<td>(reference)</td>
<td>114</td>
<td>P&lt;0.001</td>
<td>11%</td>
</tr>
<tr>
<td>Underutilization</td>
<td>44.8 (33.8, 55.8)</td>
<td>24.2 (12.5, 36.0)</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overutilization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial testing</td>
<td>43.9 (35.4, 52.5)</td>
<td>(reference)</td>
<td>18</td>
<td>P&lt;0.001</td>
<td>38%</td>
</tr>
<tr>
<td>Repeat testing</td>
<td>7.4 (2.5, 12.3)</td>
<td>−36.5 (−46.4, −26.7)</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>28.0 (22.2, 33.8)</td>
<td>−15.9 (−5.6, −26.3)</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restrictive criteria</td>
<td>44.2 (36.8, 51.6)</td>
<td>(reference)</td>
<td>26</td>
<td>P&lt;0.001</td>
<td>36%</td>
</tr>
<tr>
<td>Permissive criteria</td>
<td>12.0 (8.0, 16.0)</td>
<td>−32.2 (−40.6, −23.8)</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective criteria</td>
<td>29.0 (21.9, 36.1)</td>
<td>(reference)</td>
<td>40</td>
<td>P = 0.004</td>
<td>6%</td>
</tr>
<tr>
<td>Objective criteria</td>
<td>16.1 (11.0, 21.2)</td>
<td>−12.9 (−21.6, 4.1)</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low volume</td>
<td>32.2 (25.0, 39.4)</td>
<td>(reference)</td>
<td>36</td>
<td>P&lt;0.001</td>
<td>11%</td>
</tr>
<tr>
<td>Medium volume</td>
<td>19.8 (12.2, 27.5)</td>
<td>−12.4 (−22.9, −1.8)</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High volume</td>
<td>10.2 (2.6, 17.7)</td>
<td>−22.0 (−32.5, −11.6)</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry tests</td>
<td>19.1 (14.3, 24.0)</td>
<td>(reference)</td>
<td>86</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2%</td>
</tr>
<tr>
<td>Hematology tests</td>
<td>33.3 (20.2, 46.3)</td>
<td>14.1 (0.1, 28.1)</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiology tests</td>
<td>23.1 (6.1, 40.2)</td>
<td>4.0 (−13.7, 21.7)</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular tests</td>
<td>1.5 (0, 27.4)</td>
<td>−17.6 (−44.0, 8.8)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>25.0 (14.0, 36.1)</td>
<td>(reference)</td>
<td>17</td>
<td>P = 0.38</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Non-US</td>
<td>19.7 (15.1, 24.4)</td>
<td>−5.3 (−17.3, 6.7)</td>
<td>97</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Consequences of Inappropriate Laboratory Testing

Overutilization

- Delayed/incorrect diagnosis due to misleading test results
- Unnecessary treatment and additional diagnostic testing
- Prolonged hospitalization
- Excessive cost
- Iatrogenic anemia

Underutilization

- Delayed/incorrect diagnosis
- Delayed therapy
- Reliance on empiric therapy
A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2013 Recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)
Clinical Vignette

- 64 y/o woman with RA admitted to hospital with fever, chills, productive cough and SOB for 5 days PTA. No recent hospitalizations

- Exam: 101.3, HR 110, RR 20, 110/65

- Non-toxic, NAD

- RLL crackles

- WBC 14, 20% bands

- CXR RLL consolidation
What diagnostic test would you order?

A. Multiplex molecular respiratory panel (RFA PCR)
B. Blood culture
C. Sputum culture
D. Bronchoscopy
E. A, B, C
Respiratory Tract Infections

**Upper Respiratory Tract**
- Otitis Media
- Sinusitis
- Pharyngitis

**Lower Respiratory Tract**
- Bronchitis
- Bronchiolitis
- Pneumonia
  - Community acquired
  - Healthcare associated
CLINICAL REPORT

Principles of Judicious Antibiotic Prescribing for Upper Respiratory Tract Infections in Pediatrics

- Determine likelihood of a bacterial infection
- Weigh benefits vs. harms of antibiotics
- Implement judicious prescribing strategies

Pathogens Implicated in Respiratory Tract Infections

**Viruses**
- Adenovirus
- Bocavirus
- Coronavirus
- Metapneumovirus
- Parainfluenza virus
- Rhinovirus
- RSV
- Influenza A
- Influenza B

**Bacteria**
- *Streptococcus pneumoniae*
- *H. influenza*
- *M. catarrhalis*
- *Mycoplasma pneumoniae*
- *Legionella pneumophila*
- *Chlamidophila pneumoniae*
- Beta hemolytic Streptococci
Probability of Bacterial Pathogen in Otherwise Healthy Adults

Bacterial Pathogen Likely
- Pneumonia

Viral Pathogen Likely
- Sinusitis
- Pharyngitis
- Bronchitis
- Bronchiolitis
### Respiratory Viral Panels

<table>
<thead>
<tr>
<th>Platform</th>
<th># Targets</th>
<th>Virus</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioFire</td>
<td>20</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Genmark</td>
<td>14</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Luminex</td>
<td>20</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Verigene</td>
<td>16</td>
<td>13</td>
<td>3</td>
</tr>
</tbody>
</table>
FilmArray® Respiratory Pathogen Panel
(20 targets)

• **Viruses**
  – Adenovirus
  – Coronavirus 229E, HKU1, NL63, OC43
  – Human Metapneumovirus
  – Influenza A, A/H1, A/H1-2009, A/H3
  – Influenza B
  – Parainfluenza virus 1, 2, 3, 4
  – Human Rhinovirus/Enterovirus
  – Respiratory syncytial virus

• **Bacteria**
  – *Bordetella pertussis*
  – *Chlamydia pneumoniae*
  – *Mycoplasma pneumoniae*

**PROPOSED BENEFITS:**
- Reduce unnecessary antibiotic use
- Reduce resource utilization
- Reduce cost
- Reduce length of hospital stay
Clinical Utility of On-Demand Multiplex Respiratory Pathogen Testing among Adult Outpatients

Daniel A. Green, a, b* Letiana Hitoaliaj, c Brian Kotansky, c Sheldon M. Campbell, a, b David R. Peaper a, b

Department of Laboratory Medicine, Yale School of Medicine, New Haven, Connecticut, USA a; Pathology and Laboratory Medicine Service, West Haven Veterans Administration Hospital, West Haven, Connecticut, USA b; Pharmacy Service, West Haven Veterans Administration Hospital, West Haven, Connecticut, USA c

<table>
<thead>
<tr>
<th></th>
<th>Influenza Virus</th>
<th>Other Resp Virus</th>
<th>No Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>105</td>
<td>109</td>
<td>81</td>
</tr>
<tr>
<td>TAT (SD), hrs</td>
<td>3.2 (3.4)</td>
<td>3.4 (5.9)</td>
<td>3.1 (3.6)</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>31 (29.5%)</td>
<td>53 (48.6%)</td>
<td>40 (49.3%)</td>
</tr>
<tr>
<td>Anti-Influenza</td>
<td>80 (81%)</td>
<td>6 (5.5%)</td>
<td>2 (2.5%)</td>
</tr>
</tbody>
</table>

408 patients tested, 113 (27.6%) admitted

Daniel A. Green and others. JCM. Dec 2016. 54(12): 2950-2955
Table 2. Outcomes for hospitalized adults seeking treatment with respiratory symptoms, Ottawa, Ontario, Canada, 2004–2012*

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Study cohort, n = 24,567</th>
<th>With negative swab sample, n = 2,302</th>
<th>With positive swab sample, n = 420</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, no. (%)</td>
<td>2,550 (10.4)</td>
<td>239 (10.4)</td>
<td>40 (9.5)</td>
<td>0.594</td>
</tr>
<tr>
<td>ICU admission, no. (%)</td>
<td>2,007 (8.2)</td>
<td>341 (14.8)</td>
<td>76 (18.1)</td>
<td>0.086</td>
</tr>
<tr>
<td>Days in ICU, mean ± SD</td>
<td>8.37 ± 10.64</td>
<td>11.22 ± 12.77</td>
<td>11.70 ± 14.03</td>
<td>0.771</td>
</tr>
<tr>
<td>Hospital isolation used, no. (%)</td>
<td>7,487 (30.5)</td>
<td>1,993 (86.6)</td>
<td>396 (94.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. days in isolation, mean ± SD</td>
<td>1.79 ± 6.79</td>
<td>4.73 ± 7.65</td>
<td>5.16 ± 5.39</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*ICU, intensive care unit.
†For negative and positive swab samples.

Table 3. Laboratory, prescription, radiology, and procedure use among hospitalized patients with positive and negative NP swab samples, Ottawa, Ontario, Canada, 2004–2012*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) negative NP swab samples, n = 2,302</th>
<th>No. (%) positive NP swab samples, n = 420</th>
<th>No. (%) total swab samples, N = 2,722</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic use</td>
<td>2,204 (95.7)</td>
<td>397 (94.5)</td>
<td>2,601 (95.6)</td>
<td>0.265</td>
</tr>
<tr>
<td>Antiviral use</td>
<td>305 (13.2)</td>
<td>166 (39.5)</td>
<td>471 (17.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood cultures</td>
<td>1,813 (78.8)</td>
<td>340 (81.0)</td>
<td>2,153 (79.1)</td>
<td>0.309</td>
</tr>
<tr>
<td>Sputum cultures</td>
<td>979 (42.5)</td>
<td>167 (39.8)</td>
<td>1,146 (42.1)</td>
<td>0.291</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>147 (6.4)</td>
<td>20 (4.8)</td>
<td>167 (6.1)</td>
<td>0.202</td>
</tr>
<tr>
<td>CT scan of thorax</td>
<td>599 (26.0)</td>
<td>83 (19.8)</td>
<td>682 (25.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>1,293 (56.2)</td>
<td>229 (54.5)</td>
<td>1,522 (55.9)</td>
<td>0.532</td>
</tr>
</tbody>
</table>

*NP, nasopharyngeal; CT, computed tomography.
<table>
<thead>
<tr>
<th>Testing Location</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Department</td>
<td>11,659 (44%)</td>
</tr>
<tr>
<td>Inpatient Setting</td>
<td>10,091 (38%)</td>
</tr>
<tr>
<td>Outpatient Setting</td>
<td>3,596 (13.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>1,014</td>
</tr>
<tr>
<td>TOTAL</td>
<td>26,360</td>
</tr>
</tbody>
</table>

Estimated charges ($120-$700/test)

$3,163,200 - $18,452,000
RFAPCR included in 29 iCentra Powerplans

- CC Diabetic Ketoacidosis (DKA) ICU Admission MP
- CC Sepsis Advisor ICU Limited
- CC Sepsis ICU Admission
- CC Sepsis ICU Limited
- ED Sepsis / Severe Sepsis – Workup
- HOS Diabetic Ketoacidosis (DKA) Admission
- HOS Sepsis Admission EKM
- HOS Sepsis Advisor Limited
- HOS Sepsis Limited
- MRSA Risk: hx of MRSA; post influenza; cavitary disease; or hx of IV drug abuse
This is a non-coverage policy for multiplex PCR respiratory viral panels. The pathogen targets that compose the panels are determined by the manufacturers that make them, and do not represent specific pathogens that cause a common syndrome, or the organisms that commonly are found in a specific sample type or patient population or reflect seasonal variations. The fixed nature of these multiplex panels includes pathogens that cause infections different enough that simultaneous testing for these pathogens should be rare. Examples include Chlamydophilia (Chlamydia) pneumoniae or Bordetella pertussis in combination with rhinovirus, influenza viruses, and respiratory syncytial virus (RSV). The multiplex PCR respiratory viral panels are effectively a “one size fits all” diagnostic approach, and do not meet Medicare’s “reasonable and necessary” criteria. Non-coverage of these multiplex RCR respiratory viral panels does not deny patient access because appropriate clinician directed testing is available.
Clinical Vignette (cont.)

- Summary: Pneumonia, fever, bandemia, consolidation
- Admission RFAPCR – positive for Metapneumovirus

Discontinue antibiotics?
Hospital Course

- Ceftriaxone/azithromycin initiated due to high probability of bacterial infection
- No improvement
- Occasional runs of non-sustained ventricular tachycardia
- Respiratory culture on hospital day #5 = MRSA
- Antibiotic changed to linezolid
A 52 y/o man was admitted to Sanpete Valley Hospital with 17 days of malaise, fever, chills, night sweats and right upper quadrant pain. He had no respiratory symptoms. He was quickly diagnosed with a large, multi-loculated liver abscess.

An RFAPCR was obtained on admission despite the absence of any respiratory symptom - NEGATIVE.
A 45 y/o woman was admitted to the hospital with dry cough and shortness of breath for 4 weeks. Patient had a h/o IV drug abuse.

In the ER, patient was hypoxic and CXR was positive for diffuse, bilateral, airspace disease concerning for diffuse inflammatory process. Patient was diagnosed with advanced HIV and PJP pneumonia.

Two RFAPCRs (nasopharyngeal) were obtained on admission and were negative.

A third RFAPCR (BAL) was obtained on hospital day 6 – rhinovirus
A 36 y/o, uninsured woman admitted to Intermountain Medical Center with pleuritic chest pain and chest x-ray findings compatible with septic pulmonary emboli.

No other respiratory symptoms.

Hospital day #1 – All blood cultures positive for MSSA

TTE - tricuspid valve endocarditis.

RFAPCR obtained on admission – rhinovirus

Droplet isolation initiated despite absence of respiratory tract symptoms
Key questions to answer before ordering a lab test

- Is the test appropriate for the clinical setting?
- Will test result influence patient management?
Summary

- Molecular tests are tools that can improve patient care when used appropriately in the right setting.
- Irrational use will lead to wasted resources and an unsustainable increase in healthcare cost.
- The future of reimbursement for multiplex molecular testing is uncertain.
## Respiratory Infection Diagnostic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A/B Antigen (INAAB)</td>
<td>Rapid, low cost</td>
<td>Lower sensitivity, negative results need confirmation</td>
</tr>
<tr>
<td>Rapid RSV (RSVX)</td>
<td>Rapid, low cost</td>
<td>Lower sensitivity</td>
</tr>
<tr>
<td>Influenza A/B PCR (FLUPCR)</td>
<td>Rapid, High Sensitivity</td>
<td>High cost</td>
</tr>
<tr>
<td>Respiratory viral panel (RFAPCR)</td>
<td>Rapid, tests for everything, increased sensitivity</td>
<td>Tests for everything including less common organisms, High cost</td>
</tr>
</tbody>
</table>