What Made Sally Sick?

The FilmArray System
Multiplex PCR Technology
Objectives

• Define and discuss a syndromic approach as it relates to FilmArray and clinical patient management

• Present BioFire’s FilmArray solution to molecular testing

• Discuss the clinical benefits FilmArray delivers

• Examine FilmArray’s impact on Antimicrobial Stewardship
Define and discuss a syndromic approach as it relates to FilmArray and clinical patient management

Present BioFire’s FilmArray solution to molecular testing

Discuss the clinical benefits FilmArray delivers

Examine FilmArray’s impact on Antimicrobial Stewardship
Determining the microbial cause of disease is the cornerstone of effective disease control and prevention. However, such etiologic diagnosis has declined, compromising the quality of clinical care, surveillance, and training.

- Restrictions due to managed care
- Increasing use of empirical therapy
- Laboratory regulations (CLIA)

The Empiric Approach

• Patient presents with ID symptoms;

• Physician suspects a number of potential pathogens;

• Physician orders multiple tests, if negative must guess again; may never definitively diagnose the patient

• The Empiric Approach can sometimes be an educated best guess.
Syndromic Approach

- Clinician assesses the patient’s ID syndrome (signs+symptoms)
- Physician orders broad test that targets the syndrome
- Test results informs quick, accurate and definitive diagnosis;
- Patient begins most appropriate treatment sooner = Informed Therapy
1. (Medicine) Any combination of signs and symptoms that are indicative of a particular disease or disorder

2. A symptom is a characteristic, or characteristics indicating the existence of a condition, problem, etc.
In medicine, a differential diagnosis is distinguishing a particular disease or condition from others that present similar symptoms.[1] Differential diagnostic procedures are used by medical professionals to diagnose the specific disease in a patient.

Each individual option of a possible disease is called a differential diagnosis (for example, bronchitis could be a differential diagnosis in the evaluation of a cough that ends up with a final diagnosis of common cold).

## Why Syndromic Approach?

### Diagnostic Standpoint:
- May improve patient care and decrease hospital costs
- Accurate diagnosis when clinical presentations overlap
- Ability to detect pathogens not considered in differential
- Improved time to appropriate clinical and infection control interventions
- Epidemiology and surveillance

### Laboratory Standpoint:
- May improve efficiency and decrease testing costs
- Expand testing capabilities
- Improve time to results (no reflex testing)
- Reduce technical time (single assay)
- Reduce ancillary testing
Upper Respiratory Syndrome Signs and Symptoms

- Cough
- Wheeze
- Fever
- Congestion
- Sneezing
- Odynophagia
- Rhinorrhea
- Tonsillitis
- Pharyngitis
- Headache
- Malaise

What diagnosis might a patient receive with these symptoms?

Filmarray Respiratory Panel (Instruction booklet) Salt Lake City, UT Biofire Diagnostics; 2012:3
Upper Respiratory Tract Infection
Differential Diagnosis

Allergic Rhinitis
Asthma
Community-Acquired Pneumonia
Immunoglobulin A Deficiency
Infectious Mononucleosis
Obstructive Sleep Apnea
Otitis Media
Pediatric Retropharyngeal Abscess
Reflux Laryngitis

Acute Nasopharyngitis
Bronchiolitis
Coxsackie Virus
Group A Strep Infections
Influenza

Tuberculosis
Valley Fever
Most healthy adults may be able to infect others beginning 1 day before symptoms develop and up to 5 to 7 days after becoming sick. Some people, especially young children and people with weakened immune systems, might be able to infect others for an even longer time.

It is very difficult to distinguish the flu from other viral or bacterial causes of respiratory illnesses on the basis of symptoms alone.
Influenza viruses are constantly changing.

**Antigenic Drift** - These are small changes in the genes of influenza viruses that happen continually over time as the virus replicates.

**Antigenic Shift** – Shift is an abrupt, major change in the influenza A viruses. emerges from an animal population that is so different from the same subtype in humans that most people do not have immunity to the new (e.g. novel) virus.

Such a “shift” occurred in the spring of 2009, when an H1N1 virus with a new combination of genes emerged to infect people and quickly spread, causing a pandemic. When shift happens, most people have little or no protection against the new virus.
Coronavirus versus Influenza

- Coronaviruses are common throughout the world.
- They can infect people and animals.
- Six different coronaviruses, that scientists know of, can infect people and make them sick. They usually cause cold-like symptoms.
- But some coronaviruses, like the one that caused SARS in 2003 and the one that causes MERS, can cause severe illness.
<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
</tr>
<tr>
<td>Mucus stools</td>
</tr>
<tr>
<td>Cramping</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Bloating</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Dehydration (dry mouth, electrolyte imbalance)</td>
</tr>
</tbody>
</table>

**What diagnosis might a patient receive with these symptoms?**

FilmArray GI Instruction Booklet. Salt Lake City, UT: Biofire Diagnostics, LLC.
## Gastrointestinal Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Further Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS</td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td></td>
</tr>
<tr>
<td>Food Poisoning</td>
<td></td>
</tr>
<tr>
<td>Travelers Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Lactose Intolerance</td>
<td></td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td></td>
</tr>
<tr>
<td>- Crohn’s Disease</td>
<td></td>
</tr>
<tr>
<td>- Colitis</td>
<td></td>
</tr>
<tr>
<td>Medication reactions or SE</td>
<td></td>
</tr>
<tr>
<td>Colon Cancer</td>
<td></td>
</tr>
<tr>
<td>Diverticulosis</td>
<td></td>
</tr>
<tr>
<td>Antibiotic use</td>
<td></td>
</tr>
<tr>
<td>Hereditary disorders (e.g. cystic fibrosis, enzyme deficiencies)</td>
<td></td>
</tr>
<tr>
<td>Intussusception</td>
<td></td>
</tr>
<tr>
<td>Disorders of the thyroid (e.g. hyperthyroidism)</td>
<td></td>
</tr>
<tr>
<td>Tumors</td>
<td></td>
</tr>
<tr>
<td>Reduced blood flow to the intestine</td>
<td></td>
</tr>
<tr>
<td>Altered immune function (e.g. immunoglobulin deficiencies, AIDS, autoimmune disease)</td>
<td></td>
</tr>
</tbody>
</table>

Traditional Diagnostic Options

**Fast**\(^1,2\)
- Turnaround time
- Hands-on time

**Accurate**\(^1\)
- Sensitivity/specificity

**Comprehensive**\(^1\)
- Simultaneously identifies multiple pathogens

Molecular tests currently provide the best option for timeliness, comprehensiveness, and accuracy\(^1\)

DFA=direct fluorescent antibody; RT PCR=reverse transcriptase polymerase chain reaction.
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What does PCR mean?

1. Proton Combustible Reaction
2. Polar Charge Reaction
3. Polymerase Chain Reaction
PCR is used in molecular biology to make many copies of (amplify) small sections of DNA.

Using PCR it is possible to generate thousands to millions of copies of a particular section of DNA from a very small amount of DNA.

PCR is a common tool used in medical and biological research labs. It is used in the early stages of processing DNA for sequencing, for detecting the presence or absence of a gene to help identify pathogens during infection, and when generating forensic DNA profiles from tiny samples of DNA.

http://www.yourgenome.org/facts/what-is-pcr-polymerase-chain-reaction
Five core ‘ingredients’ are required to set up a PCR

- The DNA template to be copied
- Primers, short stretches of DNA that initiate the PCR reaction
- DNA bases (A, C, G and T) are the building blocks of DNA and are needed to construct the new strand of DNA
- Taq polymerase enzyme to add in the new DNA bases
- Buffer to ensure the right conditions for the reaction
How does PCR work?

PCR involves a process of heating and cooling called thermal cycling which is carried out by machine. There are three main stages:

- **Denaturing** – when the double-stranded template DNA is heated to separate it into two single strands.

- **Annealing** – when the temperature is lowered to enable the DNA primers to attach to the template DNA.

- **Extending** – when the temperature is raised and the new strand of DNA is made by the Taq polymerase enzyme.

http://www.yourgenome.org/facts/what-is-pcr-polymerase-chain-reaction
Reverse transcription polymerase chain reaction (RT-PCR), a variant of polymerase chain reaction (PCR), is a technique commonly used in molecular biology to detect RNA expression.

RT-PCR is sometimes confused with real-time polymerase chain reaction (qPCR), but they are separate and distinct techniques.

Traditional PCR is used to exponentially amplify target DNA sequences. RT-PCR is used to clone expressed genes by reverse transcribing the RNA of interest into its DNA complement through the use of reverse transcriptase. Subsequently, the newly synthesized cDNA is amplified using traditional PCR.
### The State of Current Molecular Tests

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detect viruses that cannot be cultured</td>
<td>Complicated; technically demanding</td>
</tr>
<tr>
<td>Detect multiple organisms in a single procedure</td>
<td>Require specialized technologists</td>
</tr>
<tr>
<td>High sensitivity and specificity</td>
<td>Long turnaround time (6–8 hours)</td>
</tr>
<tr>
<td></td>
<td>Generally only performed during daytime hours in virology/molecular labs in large, tertiary medical centers</td>
</tr>
</tbody>
</table>
Rapid Molecular Companies

- Nanosphere
- GenMark Dx
- Luminex
- Cepheid
BioFire DX: Over 20 Years of Innovations

1990: Idaho Technology, Inc.

1996: Molecular Biology Tools
  • LightCycler®

2000: Applied PCR
  • BioThreat Testing
  • Food Testing

2011: Respiratory Panel

2013: Blood Culture Identification Panel

2014: Gastrointestinal Panel

2015: Meningitis Panel
FilmArray – Sample to Result
How Does the FilmArray Work?

Simple: Only 2 minutes of hands-on time
Easy: No precise pipetting required
Fast: Run time of only 1 hour

The FilmArray Pouch

Self-contained Pouch:

- Stores all reagents
- Performs the extraction, amplification, and detection
- Is a closed system, minimizing contamination
How the FilmArray Works

Sample Extraction & Preparation

1st Stage Multiplex PCR

2nd Stage PCR

Reagent Storage

Chemical Circuit Board
How the FilmArray Works

Two Internal Controls

- RNA Process Control - Freeze-dried Schizosaccharomyces pombe organism, which is re-suspended with specimen

- PCR II Control - DNA template spotted on the array
Automated Protocol

- Bladders inflate over blisters to move liquid
- Pistons open and close the channels
- Plungers deliver reagents
Automated Results Analysis

- 102 individual 2\textsuperscript{nd} stage PCR wells
- Each well contains one reaction
- Melt curves generated for each well
Automated Results Analysis

• All targets tested in triplicate
• Two out of three wells must be positive
• Melting peaks must fall within their specific range
• Melting peaks must be significantly similar to each other

*Bordetella pertussis*
A Syndromic Approach to a Rapid and Accurate Diagnosis

**Easy**
- 2 minutes of hands-on time

**Fast**
- Run time of about 1 hour

**Comprehensive**
- Tests for a variety of pathogens that cause respiratory, blood, gastrointestinal and meningitis/encephalitis infections, as well as antimicrobial resistant genes

**Accurate**
- High sensitivity and specificity
Taking Out the Guesswork: Easy-to-Interpret Results

- Automated analysis
- Clear and easy-to-read results

FilmArray® Respiratory Panel

Run Summary

- Sample ID: RYNAND0232
- Detected: Influenza A H1-2009
  - Respiratory Syncytial Virus
- Equivocal: None
- Run Date: 21 Jun 2013 7:34 PM
- Controls: Passed

Result Summary

- Not Detected: Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Human Metapneumovirus, Human Rhinovirus/Enterovirus
- Detected: Influenza A H1-2009, Influenza B, Parainfluenza Virus 1, Parainfluenza Virus 2, Parainfluenza Virus 3, Parainfluenza Virus 4, Respiratory Syncytial Virus, Bordetella pertussis, Chlamydia pneumoniae, Mycoplasma pneumoniae

Run Details

- Pouch: Respiratory Panel v1.7
- Run Status: Completed
- Serial No.: 003457672
- Lot No.: 114612
- Protocol: NPS v2.0
- Operator: KMRAP
- Instrument: ITI FA "FA2004"
Samples arrive 1 per hour for 24 hours

- 2 random access FilmArray instruments
  - Samples started within 10 minutes of arrival, run time of 65 minutes
- 1 GenMark eSensor® system (batching)
  - 4 batches of 6 samples each, workflow of 6 hours

<table>
<thead>
<tr>
<th></th>
<th>Average Turnaround Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>FilmArray</td>
<td>75 minutes</td>
</tr>
<tr>
<td>eSensor</td>
<td>8.5 hours</td>
</tr>
</tbody>
</table>

Decisions that may be needed within the initial 8.5 hours:

Admission? Isolation? Cohorting? Antiviral or antibiotic therapy?

In a comparison between the FilmArray and DFA at a core laboratory at Seattle Children’s Hospital, 81% of patients with influenza received oseltamivir within 3 hours of ED discharge.

<table>
<thead>
<tr>
<th>Method</th>
<th>Total Volume</th>
<th>Mean Turnaround Time, Hours</th>
<th>% Samples Completed in &lt;2 Hours; &lt;3 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>FilmArray*</td>
<td>2537</td>
<td>1.6</td>
<td>82; 95</td>
</tr>
<tr>
<td>DFA†</td>
<td>1399</td>
<td>7</td>
<td>0; 2</td>
</tr>
</tbody>
</table>

- Three FilmArray instruments potentially saved 900 hours of ED use over 4 months

* From 12/14/11-4/19/12.
† From 12/14/10-4/19/11.
DFA=direct fluorescent antibody; ED=emergency department.
Disease-Specific Panels Provide Comprehensive Coverage for Syndromic Testing

- **Respiratory Panel**
  - 20 Targets
  - 3 bacteria
  - 17 viruses

- **Blood Culture Identification Panel**
  - 27 Targets
  - 19 bacteria
  - 5 yeast
  - 3 antibiotic-resistance genes

- **Gastrointestinal Panel**
  - 22 Targets
  - 13 bacteria
  - 5 viruses
  - 4 parasites

- **Meningitis/Encephalitis Panel**
  - 14 Targets
  - 6 bacteria
  - 7 viruses
  - 1 yeast
Respiratory Panel (RP)

Viruses
Adenovirus
Coronavirus HKU1
Coronavirus NL63
Coronavirus 229E
Coronavirus OC43
Human Metapneumovirus
Human Rhinovirus/Enterovirus
Influenza A
Influenza A/H1
Influenza A/H3
Influenza A/H1-2009
Influenza B

Parainfluenza 1
Parainfluenza 2
Parainfluenza 3
Parainfluenza 4
Respiratory Syncytial Virus

Bacteria
Bordetella pertussis
Chlamydia phila pneumoniae
Mycoplasma pneumoniae

FDA-cleared for the first time.
# How Does FilmArray Compare for RP?

<table>
<thead>
<tr>
<th></th>
<th>BIOS</th>
<th>Nanosphere</th>
<th>GenMarkDx</th>
<th>Luminex</th>
<th>Cepheid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample-to-Answer?</td>
<td>✓</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>✓</td>
</tr>
<tr>
<td>Comprehensive Panels</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>No</td>
</tr>
<tr>
<td>Hands-on Time</td>
<td>2 minutes</td>
<td>~5 minutes</td>
<td>55 minutes</td>
<td>45 minutes</td>
<td>2 minutes</td>
</tr>
<tr>
<td>Total Time to Result</td>
<td>1 hour</td>
<td>2.5 hours</td>
<td>6 hours</td>
<td>6 hours</td>
<td>1 hour</td>
</tr>
<tr>
<td>Viral Pathogens</td>
<td>17</td>
<td>7</td>
<td>14</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Bacterial Pathogens</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Popowitch EB et al. An Analytical Comparison of Four Commercial Respiratory Virus Panels. Presented at 28th Annual Clinical Virology Symposium and Annual Meeting of the Pan American Society for Clinical Virology (PASCV); April 22-25, 2012; Daytona Beach, FL.
Who invented PCR?

1. Watson & Crick
2. Kary Mullis
3. Roche Company

He was awarded the Nobel Prize in Chemistry in 1993 for his pioneering work.
Gastrointestinal (GI) Panel

FDA-cleared for the first time.

**Bacteria**
- Campylobacter (*jejuni, coli, and upsaliensis*)
- *Clostridium difficile* (Toxin A/B)
- *Plesiomonas shigelloides*
- *Salmonella*
- *Vibrio (parahaemolyticus, vulnificus, and cholerae)*
  - *Vibrio cholerae*
- *Yersinia enterocolitica*

**Diarrheagenic E. coli/Shigella**
- Enteroaggregative *E. coli* (EAEC)
- Enteropathogenic *E. coli* (EPEC)
- Enterotoxigenic *E. coli* (ETEC)
- Shiga-like toxin-producing *E. coli* (STEC)
  - *E. coli* O157
- Shigella/Enteroinvasive *E. coli* (EIEC)

**Parasites**
- *Cryptosporidium*
- *Cyclospora cayetanensis*
- *Entamoeba histolytica*
- *Giardia lamblia*

**Viruses**
- Adenovirus F 40/41
- *Astrovirus*
- Norovirus GI/GII
- Rotavirus A
- Sapovirus (I, II, IV, and V)
## How Does FilmArray Compare for GI?

<table>
<thead>
<tr>
<th></th>
<th>FilmArray</th>
<th>Luminex(^1)</th>
<th>HOLOGIC(^2,3)</th>
<th>BD MAX(^4,5)</th>
<th>Nanosphere(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample-to-answer?</td>
<td>✔</td>
<td>No</td>
<td>No</td>
<td>✔</td>
<td>No</td>
</tr>
<tr>
<td>Comprehensive panel</td>
<td>✔</td>
<td>✔</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hands-on time</td>
<td>2 minutes</td>
<td>45 minutes</td>
<td>&lt;30 minutes</td>
<td>1.5 minutes</td>
<td>~5 minutes</td>
</tr>
<tr>
<td>Total time to result</td>
<td>1 hour</td>
<td>5 hours</td>
<td>4 hours</td>
<td>&lt;3 hours</td>
<td>~2 hours</td>
</tr>
<tr>
<td>Bacteria</td>
<td>14</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Viruses</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parasites</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**FilmArray® Meningitis/Encephalitis Panel**

**Bacteria**
- *Escherichia coli K1*
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

**Viruses**
- *Cytomegalovirus (CMV)*
- Enterovirus (EV)
- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
- *Human herpesvirus 6 (HHV-6)*
- *Human parechovirus (HPeV)*
- *Varicella zoster virus (VZV)*
  *FDA-cleared for the first time*

**Yeast**
- *Cryptococcus neoformans/gattii*

*FDA-cleared through the de novo classification process*

This indicates that there are no other similar tests available in the US, and establishes BioFire Diagnostics as the leader in syndromic testing for meningitis/encephalitis

**Overall 94.2% Sensitivity and 99.8% Specificity**

1. FilmArray Meningitis/Encephalitis Panel: Instruction Booklet downloadable at https://www.online-ifu.com/ITI0035/3831/EN
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Clinical and Economic Consequences of Respiratory Infections In the United States

- 25,000,000 family physician consultations¹
- 1,026,476 hospitalizations due to upper respiratory tract infections between 1998 and 2006²
- $40 billion estimated annual cost of non-influenza–related viral respiratory tract infections³

Case Study 1: Erin M.

It is mid-October. Erin presents to the ER with a fever and general body aches. Her mother tells you that she hasn’t yet received a flu vaccine.

- **Age:** 3
- **Chief complaint:**
  - Low energy
  - Dry coughs
  - Body aches
- **Temperature:** 100.3°F
- **History of present illness:** symptoms started 1 day ago, starting with minor body aches then progressed into fever and coughs
- **Other information:** Recent URTI outbreak at daycare

How could the FilmArray GI Panel have helped guide Amy’s diagnosis and treatment?

ER=emergency room; URTI=upper respiratory tract infection.
Infectious disease syndromes have many potential causes. Testing for only 2-3 will lead to many missed infections.
Improve Care for Elderly Patients

Respiratory infections, such as RSV, HMPV, and influenza are difficult to differentiate in older adults due to similar clinical presentations and seasonal patterns\(^1\)

Timeliness

Timely antiviral treatment can improve patient outcomes and reduce mortality

*Early use of antivirals is associated with rapid viral clearance, fewer symptoms, reduced progression to pneumonia, and reduced mortality\(^2\)*

Accuracy

Sensitivity of rapid tests and viral culture is lower among older patients\(^1\)

*Accurate diagnostic tests are required to verify illnesses that cannot be confirmed by symptoms or current tests*

HMPV=human metapneumovirus; RSV=respiratory syncytial virus.
In a letter to CA Acute Care Hospitals (Dec. 15, 2015), CDPH writes:

- “Real-time reverse transcription polymerase chain reaction (rRT-PCR) diagnostic testing and prompt empiric antiviral therapy for patients hospitalized with suspected influenza.”

- State that there are “Limitations of rapid testing: In contrast to rRT-PCR, rapid influenza diagnostic tests (RIDT) have limited sensitivity. Therefore, falsely negative RIDT results can occur, especially when influenza is widespread. Falsely positive results may occur when influenza activity is low.”

- Recommends that “Empiric therapy with a neuraminidase inhibitor should be initiated promptly while awaiting rRT-PCR results in patients hospitalized with suspected influenza.”
The FilmArray Provides Accurate Results to Improve Patient Management

Detect a broader range of pathogens, including coinfections

- In a comparison between the FilmArray RP and Prodesse assays, 78.6% of patients tested positive for a respiratory infection by the FilmArray, compared to 23.4% by Prodesse
  - This discrepancy was largely attributed to the larger number of targets detected by the FilmArray using one assay versus Prodesse using five assays

- In 192 patient specimens, the FilmArray panel detected 155 pathogens that are not included in the Prodesse assays, and more coinfections compared with Prodesse (28 vs 3)

Improve patient isolation and cohorting

- Accurately identifying etiologic agents can inform isolation and cohorting to minimize cross infection
- Ruling out infections such as influenza can verify that strict isolation procedures are not needed for urgent surgeries

Impact of FilmArray RP on Patient Outcomes of Children with Acute Respiratory Tract Illness

A retrospective, single-center study conducted at a tertiary referral center, Children’s Healthcare of Atlanta, assessed the clinical and economic impact of utilizing the FilmArray RP versus traditional PCR analysis.

In children with an acute respiratory tract illness admitted to the hospital who were not on a predefined protocol, the FilmArray RP panel reduced:

- Time to Test Result by 65%
- Length of stay by 0.3 days for patients with a positive result
- Hospital costs of $231/patient and cost of antibiotic use/patient by $17

And increased:

- The % of test results reported while the patient was still in the ED from 13.4% to 51.6%

"The RRP decreases the duration of antibiotic use, the length of inpatient stay, and the time in isolation."
Impact of FilmArray RP on Patient Outcomes of Adults in the ICU

A retrospective, single-center study conducted at Geisinger Medical Center on the clinical and economic impact in 736 adult ICU patients.

Statistically significant improvements (p<0.05) were observed via reductions in:

- 28-day all cause mortality (when results reported >7 hours)
- Collect to Result (CTR) time
- ED wait times per pre-admission visit
- ICU days per ICU visit
- Length-of-Stay
- Antibiotic days per visit
- Ventilator days per visit
- Total number of laboratory orders
- Total cost per visit

"The FilmArray is a random access instrument which eliminates the need for batch testing and may significantly reduce CTR time in a variety of healthcare settings."
Multiple Studies Prove the Clinical and Economic Benefits of FilmArray RP

Implementation of FilmArray Respiratory Viral Panel in a Core Laboratory Improves Testing Turnaround Time and Patient Care

- The mean turnaround time decreased to 1.6 hours vs 7 hours using DFA
- 81% of patients were administered or given a prescription for oseltamivir while in the ED or within 3 hours of ED discharge
- Patients tested with FilmArray RP were placed into cohorts effectively.
- The FilmArray RP resulted in a potential savings of 900 hours in ED boarding time.

“The implementation of the FilmArray respiratory panel in our laboratory significantly decreased the time required to detect and report respiratory viruses. Patients with influenza A and B were treated rapidly and appropriately. Detection of other viral agents assisted physicians in the differential diagnosis of respiratory syndromes and isolation of patients admitted to the hospital. We implemented a molecular-based efficient diagnostic test in our core laboratory for the first time, marking a new era in pediatric clinical laboratory medicine.”

Break Time
Gastrointestinal Infections: Mortality and Costs

211–375 million episodes of diarrheal illness occur in the United States annually, resulting in:

- 73,000,000 physician consultations
- 1,800,000 hospitalizations
- 3,100 deaths
- $6 billion spent on medical care and lost productivity

Amy M.

- Amy presented to the emergency room with bloody diarrhea, fever, and abdominal pain and tenderness
- On initial diagnosis, Amy was suspected to have *Shigella* infection. She was admitted to the hospital, and ciprofloxacin therapy was initiated, prior to completion of stool culture results
- Amy is now in the ICU, having progressed to hemolytic uremic syndrome (HUS)

**History of present illness:**
- Symptoms started 5 days ago
- Bloody diarrhea from Day 3
- HUS developed following ciprofloxacin therapy
- Kidney failure

**Other information:** recent diarrhea outbreak at daycare center

**Case Study 2: Amy M.**

How could the FilmArray GI Panel have helped guide Amy’s diagnosis and treatment?
Laguna Middle School canceled its annual eighth grade dance Friday after about 80 eighth graders and one teacher came down with a highly contagious norovirus.

Health Officer, Dr. Penny Borenstein with the San Luis Obispo County Public Health Department said “It looks like probably something at the luncheon, or maybe even someone, might have caused it, though that is just a guess.”

The highly contagious virus causes diarrhea, vomiting and stomach pain, and usually lasts one to three days. It can be caught from an infected person, through contaminated food or water, or by touching contaminated surfaces.

Consequences of Misdiagnosis and Mistreatment of GI Infections

Potential outcomes of incorrect diagnosis and treatment

1. Worsened illness
   - Disease complications
   - Suprainfection
   - Prolonged carrier state
   - Clinical relapse

2. Postinfectious sequelae
   - Reactive arthritis
   - Guillain-Barré syndrome
   - Irritable bowel syndrome
   - Malnutrition

3. Unnecessary side effects
   - GI distress
   - Rash
   - Dizziness

4. Antibiotic resistance
   - Increasing public health concern
   - Global health security threat

Early diagnosis facilitates timely and appropriate therapeutic interventions that can alleviate symptoms and prevent secondary transmission

A Fast and Accurate Diagnosis Can Ensure Appropriate Treatment

The FilmArray GI panel tests for 22 pathogens simultaneously and is capable of rapidly distinguishing pathogens that can be misdiagnosed due to overlapping clinical symptoms, such as *Shigella* and *E. coli* STEC O157.

In Amy’s case, the FilmArray GI panel would have detected *E. coli* STEC O157 infection several days faster than traditional stool culture methods.

The correct diagnosis would have informed appropriate treatment, and may have prevented progression to HUS.

HUS=hemolytic uremic syndrome.
A Fast and Accurate Diagnosis Can Ensure Appropriate Treatment

**IDSA *E. coli* STEC treatment guidelines (2001):**

- Antibiotics and antimotility agents are not recommended for treating this infection\(^1\)
  - Antibiotic treatment is associated with an increased risk of developing HUS\(^1\)

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**Incidence of HUS in *E. coli* STEC O157:H7 Infection\(^2\)**

- 6% of patients develop HUS within 2 to 14 days of onset of diarrhea\(^2\)
- 15.6% (range 7.5%–34.8%) of patients receiving antibiotics developed HUS\(^2\)

HUS=hemolytic uremic syndrome; IDSA=Infectious Diseases Society of America.

Prospective analysis of 1,556 stool specimens conducted between May and September, 2013. The FilmArray GI Panel detected organisms in 53.5% (832/1556) of the prospective specimens.

In positive specimens:

- **68.5%** single organism detected
- **31.5%** multiple organisms detected

Number of Organisms Detected:

- 2 organisms: 76%
- 3 organisms: 19%
- 4 organisms: 3%
- 5 organisms: 1%
- 6 organisms: 1%
David presents to his primary care physician with abdominal pain, vomiting and nausea, weight loss, and extreme fatigue.

- **Age:** 28
- **Chief complaints:**
  - Abdominal pain
  - Vomiting and nausea
  - Extreme fatigue
- **Temperature:** 98.6°F

**History of present illness:**
Symptoms have been ongoing for 2 weeks.

**Other information:** David recently returned from traveling in Peru.

How would you approach diagnostic testing in this patient? What advantages would the FilmArray GI Panel provide?
Accurate Analyses of Multiple Agents Simultaneously Can Identify Coinfection

The causative agents of travelers’ diarrhea can be difficult to differentiate due to their overlapping clinical patterns and geography¹.

*Cyclospora cayetanensis* and *Cryptosporidium* are suspected causative agents due to David’s recent travel to Peru

Both parasites are:

- Endemic to Peru¹,²
- Transmitted via the ingestion of sporulated oocysts from contaminated produce, fruits, and water¹,²
- Overlapping in clinical profile³

---

Accurate Analyses of Multiple Agents Simultaneously Can Identify Coinfection

*Cyclospora cayetanensis* is not routinely requested/tested for in O&P examinations.¹

Misidentification of *Cyclospora cayetanensis* as *Cryptosporidium* by modified acid-fast-stained fecal smear sometimes occurs as a result of their similar appearance.²,³

O&P=ova and parasite.
## Accurate Analyses of Multiple Agents Simultaneously Can Identify Coinfection

### Modified Acid-Fast Stained Fecal Smear
- Labor-intensive, lacks sensitivity and specificity\(^1\)
- Repeat testing required due to intermittent low-grade oocyte shedding\(^2\)
- Poor uptake of histological stains by oocytes\(^1\)
- 0.4% and 1.7% recovery rates of *Cyclospora cayetanensis* and *Cryptosporidium*, respectively\(^3\)

### Molecular Biology
- Improved diagnostic performance, especially in patients with low parasite burden and intermittent shedding\(^3\)
- Ability to test for multiple pathogens simultaneously\(^4\)
- Resolves problem of misdiagnosis of *Cyclospora cayetanensis* as *Cryptosporidium*\(^5\)
- More rapid diagnosis\(^4\)

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The FilmArray GI Panel detected an outbreak of *Cyclospora cayetanensis* prior to the CDC\(^4\)

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Meningitis/Encephalitis

**Meningitis** is defined as inflammation of the meninges and is characterized by an increased number of white blood cells in the CSF\(^1,2\)

**Encephalitis** is inflammation of the brain parenchyma that causes neurologic dysfunction\(^3,4\)

Meningitis and encephalitis can be caused by a number of infectious agents, including bacteria, viruses, parasites, mycobacteria and fungi, as well as noninfectious causes, and often present with very similar symptoms\(^5\)
Meningitis and encephalitis can occur suddenly in healthy people\(^1\). Populations at higher risk of contracting meningitis and encephalitis include\(^2\):

- Infants
- Immunocompromised
- Military personnel
- College students
- Travelers
Meningitis/Encephalitis: US Mortality and Costs

- In 2006, >72,000 meningitis-related hospitalizations were recorded in the US, totaling $1.2 billion in hospital costs

<table>
<thead>
<tr>
<th></th>
<th>Annual number of hospitalizations</th>
<th>Mortality rate</th>
<th>Mean cost per hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meningitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td>15,700¹</td>
<td>8.0%¹</td>
<td>$33,100¹</td>
</tr>
<tr>
<td>Viral</td>
<td>39,300¹</td>
<td>0.6%¹</td>
<td>$6,800¹</td>
</tr>
<tr>
<td>Fungal</td>
<td>5,300¹</td>
<td>9.1%¹</td>
<td>$29,000¹</td>
</tr>
<tr>
<td><strong>Encephalitis</strong></td>
<td>20,258²</td>
<td>5.8%²</td>
<td>$48,852²</td>
</tr>
</tbody>
</table>
Delayed Treatment Is Associated With Increased Morbidity and Mortality

- The causative agents of meningitis or encephalitis should be rapidly identified to guide appropriate patient management but are many times impossible to identify based on clinical indications alone due to overlapping symptoms\(^1,2\)
- Delays in appropriate therapy can be associated with adverse outcomes\(^1\)

**Bacterial\(^2\)**
- Permanent brain and nerve damage
- Behavioral changes
- Cognitive disabilities
- Lack of muscle control
- Seizures

**Viral\(^2,3\)**
- Brain damage, including behavioral and personality changes and memory and speech problems
- Focal neurological signs
- Seizures

**Fungal\(^4\)**
- Increased intracranial pressure
- Hydrocephalus
- IRIS
- Blindness, sometimes with optic atrophy

Early diagnosis facilitates timely and appropriate therapeutic interventions and can minimize the risks of adverse outcomes and mortality\(^2\)
Diagnosing Meningitis and Encephalitis: Traditional Diagnostics

- CSF analysis is a fundamental method in diagnosing meningitis or encephalitis, but often only small volumes are obtained by lumbar puncture, limiting testing options\(^1-3\)
- CSF samples are considered high-priority and are processed immediately\(^4\)

**CSF Examination\(^5\)**
- Cell count
- Protein
- Glucose

**CSF Culture\(^5,6\)**
- Pathogen-specific media
- Bacterial culture
- Viral culture
- Fungal culture

**Gram Stain\(^7\)**
- Crystal violet
- Iodine
- Alcohol
- Safranin

**India Ink Stain\(^5\)**

**Rapid Latex Agglutination Test\(^8\)**
- Positive
- Negative

**Traditional PCR\(^5\)**
Challenges in Diagnosing Meningitis and Encephalitis Infections

- Meningitis and encephalitis often present with similar symptoms, sometimes as a flu-like illness.
- Since the causative agents are often not distinguishable based on clinical symptoms alone a specific diagnosis often needs accurate and comprehensive laboratory testing.

- Time-consuming
- Technically complex/requires specific expertise
- Accuracy may be affected by antibiotic administration
- Lack sensitivity and specificity
- Small volume of CSF obtained
- Physician must choose which tests to select based on symptoms and available CSF volume
- Need to order multiple tests specific for suspected organisms

Rapid diagnosis of the causative agent of infections and appropriate treatment decisions can improve patient outcomes and decrease healthcare costs\textsuperscript{1,2}

**Provider**
- Provides more comprehensive testing\textsuperscript{4}
- Informs improved quality of care\textsuperscript{2}
- Guides appropriate follow-up\textsuperscript{3}

**Patient**
- Shortened illness\textsuperscript{1}
- Shorter hospital visits\textsuperscript{2}
- Reduced morbidity\textsuperscript{1}
- Prevents secondary transmission\textsuperscript{1}

Fast results\textsuperscript{3}
Comprehensive coverage\textsuperscript{3}
Accurate pathogen identification\textsuperscript{3}

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3. FilmArray GI [Instruction Booklet]. Salt Lake City, UT: BioFire Diagnostics, LLC.
Objectives

• Define and discuss a syndromic approach as it relates to FilmArray and clinical patient management

• Present BioFire’s FilmArray solution to molecular testing

• Discuss the clinical benefits FilmArray delivers

• Examine FilmArray’s impact on Antimicrobial Stewardship
POP QUIZ!

Alexander Fleming discovered which antibiotic in 1928?

1. Penicillin
2. Vancomycin
3. Doxycycline
Prevent Antibiotic Resistance

According to the Institute of Medicine, antibiotic resistance is one of the key microbial threats to health in the US.

Implications of Antibiotic Resistance

- Increases mortality and morbidity from untreatable diseases
- Increases risk of global spread of pathogens
- Results in longer, more frequent hospital stays
- Limits drug options at a time when pharmaceutical companies are developing fewer new antimicrobials
- Increases cost of research for new drugs

What is Antibiotic Stewardship?

- 20-50% of all antibiotics prescribed in U.S. acute care hospitals are either unnecessary or inappropriate.

- The misuse of antibiotics has also contributed to the growing problem of antibiotic resistance, which has become one of the most serious and growing threats to public health.

- Improving the use of antibiotics is an important patient safety and public health issue as well as a national priority.

http://www.cdc.gov/getsmart/healthcare/implementatio
Core Elements of Hospital Antibiotic Stewardship Programs

- Leadership Commitment: Dedicating necessary human, financial and information technology resources
- Accountability: Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician leader is effective
- Drug Expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use
- Action: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours)
- Tracking: Monitoring antibiotic prescribing and resistance patterns
- Reporting: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff
- Education: Educating clinicians about resistance and optimal prescribing

http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html
Some people often require no treatment since many infections are self-limited. The main treatment needed is hydration, in the form of either oral or intravenous hydration.

Several studies suggest that antibiotics should not be used because they lead to a more severe disease. This increase in severity is believed to be related to the damaging effect of the antibiotic on the bacteria, causing the damaged bacteria to release more toxins.

The use of antibiotics has been reported to markedly increase the incidence of HUS (17-fold).

HUS=hemolytic uremic syndrome; IDSA=Infectious Diseases Society of America.
http://www.emedicinehealth.com/e_coli_escherichia coli_0157h7_e_coli_0157h7/page6_em.htm
Summary: Outcomes of Inappropriate or Delayed Care

- Death rate for patients with ARIs was two-fold higher than for those without ARIs. \(^1\)

- The misuse of antibiotics costs the US healthcare system over $20 billion each year. \(^2\)
  - US households lost approximately $35 billion in 2000 to antibiotic-resistant infections, including lost wages, extended hospital stays, and premature deaths. \(^2\)

- Delayed treatment of influenza can result in complications including pneumonia and exacerbations of underlying pulmonary and cardiac disease. \(^3\)
  - From 2008 to 2013, death rates due to influenza and pneumonia exceeded the epidemic threshold multiple times. \(^4\)

ARI=antibiotic-resistant infection.

The Future of FilmArray

The FilmArray Panels

- Respiratory Panel
  FDA-Cleared May 2011
- BCID Panel
  FDA-Cleared May 2014
- GI Panel
  FDA-Cleared June 2013
- Meningitis Panel
  FDA Clearance Oct 2015
- Lower Respiratory Panel
  In development

BCID=blood culture identification; GI=gastrointestinal.
An ounce of prevention is worth a pound of cure.

Questions?