MULTIPLEX PCR FOR GASTROENTERITIS

TYLER RADKE, MLS(ASCP)
LABORATORY MANAGER
What are you performing today?

- A – Multiplex NAAT
- B – Stool Culture w/ NAAT
- C – Stool Culture w/ kit testing
- D – Single Assay NAAT
- E – Other
EXPECTED IMPACT

GENERAL ASSUMPTIONS

• COMPARITIVELY EXPEDITIOUS
  ▪ Equal processing time
  ▪ Less manual interpretation time
  ▪ Less clerical time
  ▪ Faster Turn-Around-Time (TAT)

• IMPROVED DETECTION
• IMPROVED PATIENT OUTCOMES
• PHYSICIAN & PATIENT SATISFIER
• COST NEUTRAL
IMPROVED DETECTION
What was the most commonly detected organism on the multiplex PCR Panel?

Improved Detection

- A – Enteropathogenic E. coli
- B – Campylobacter spp.
- C – Salmonella spp.
- D – Entamoeba histolytica
- E – Norovirus
• > 33% positivity rate on 6311 samples tested (excludes EPEC & C. diff)
  ▪ 16 cases of Vibrio spp.
  ▪ 15 cases of Plesiomonas shigelloides
  ▪ 21 cases of E. coli 0157
  ▪ 31 cases of Cyclospora
  ▪ 33 cases of Yersinia enterocolitica
  ▪ 89 Adenovirus
  ▪ 110 Astrovirus
  ▪ 119 cases of Cryptosporidium
  ▪ 120 cases of Rotavirus
  ▪ 123 cases of Giardia lamblia
  ▪ 174 Sapovirus

• Additional Questions!
IMPROVED OUTCOMES
Improved Patient Outcomes

- Heavily data dependent
- Earlier intervention impacting downstream consequences (work days lost)

![Time to Result](chart1)

![Interface Impact](chart2)

- PCR Collect to Final
- Stl Culture

- Manual
- W/ Autover
Improved Patient Outcomes

• Earlier initiation of targeted antimicrobial therapy
• Earlier discontinuation of empirical antimicrobial therapy
• Less likely to undergo endoscopy or abdominal radiology
• Less likely to be prescribed any antibiotic

• Clinical Impact of a Multiplex Gastrointestinal Polymerase Chain Reaction Panel in Patients With Acute Gastroenteritis – Cybulski et al.
• Impact of Gastrointestinal Panel Implementation on Health Care Utilization and Outcomes – Axelrad et al.
Case Study

- 7-year old female with Hx of cerebral palsy presents for vomiting, diarrhea of 5 days, and lethargy. No signs of fever, cough, dysuria, myalgia, neck pain/stiffness, adenopathy, etc.
- Physical exam mostly unremarkable.
- WBC 23.6 with 37% bands, remaining components reflective of dehydration.
- Creatinine 1.05, Bilirubin 1.4, albumin 2.9
- Patient given bolus of fluid, placed on maintenance, and given Zofran.
- Pediatric Hospitalist consulted, patient admitted to Peds Unit with impression of gastroenteritis and moderate dehydration.

PLAN:
- Fluids, electrolytes, and nutrition
- Start on Ceftriaxone given elevated bands and wait for Blood/Urine cultures to complete
- Continue treatment of seizure disorder
Case Study

Day 2:
• Overnight fluid resuscitation did not produce expected outcomes
• BUN up to 54, Creatinine up to 2, WBC down to 17, Platelets down to 40
• Continued Tachycardia
• Stool PCR ordered

E. Coli 0157

Discharge Diagnosis:
• Gastroenteritis secondary to E. coli 0157
• Thrombocytopenia likely secondary to hemolytic uremic syndrome
• Renal failure
• Admitted to ICU
Patient Outcomes – Unintended Consequences

1. **Additional prescribing of antibiotics**
   a) Patient and Insurer Cost
   b) Naïve bacteria exposed to antibiotics $\rightarrow$ environmental pressure $\rightarrow$ resistance development
   c) Predisposition to acquire C. difficile
   d) Antibiotic side effects

2. **Unnecessarily prescribing antibiotics**
   a) Pediatric population with dual detections
PROVIDER & PATIENT SATISFACTION
**Satisfaction**

- **Providers**
  - Faster results
  - More detections
  - Earlier interventions

- **Patients**
  - Faster results
  - More answers provided
  - Quicker to treatment

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**THE BLAME GAME**
Have you experienced problems with reimbursement or patient cost?

- A – YES
- B – NO
- C – I Don’t Know
- D – Other

Improved Detection
Monetary Satisfaction

- Spreadsheet of all In-Network Payers and their rate by CPT code
- Determine distribution of CPT charge code by Network Payer
- Determine amount of money “left on the table”
- Get administration approval
Approximately how much do you charge for a multiplex panel?

- A $100-$500
- B $500-$1000
- C $1000-$1500
- D >$1500
- E – Don’t know

Improved Detection
CMS LCD Ruling

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This contractor will provide limited coverage for Gastrointestinal Pathogen (GIP) molecular assays identified by multiplex nucleic acid amplification tests (NAATs), and will limit GIP coverage in immune competent beneficiaries up to 5 bacterial targets which represent the top 90-95% of foodborne infections ([incidence of infection per 100,000 population]in decreasing incidence): Salmonella [15.89]; Campylobacter [12.97]; Shigella [5.53]; Cryptosporidium [3.31]; Shiga toxin producing E. coli (STEC) non-O157 [1.64] and STEC O157 [.95].

In addition, when there is a clinical concern for Clostridium difficile colitis, this contractor will cover up to 11 targets if Clostridium difficile is one of the organisms tested for.

Testing for 12 or more organisms will only be covered in critically ill or immunosuppressed patients.

In immune competent individuals, most people with Cryptosporidium, a parasitic disease, will recover without treatment. The pathogens in some of the GIP panels are determined by the manufacturers that make them, and do not represent specific pathogens that cause a common age-based syndrome, or represent organisms that commonly are found in a specific sample type, patient population or reflect community acquired foodborne infections. Because of the unique clinical circumstances of immune compromised patients, ICU patients, and HIV positive patients with diarrhea, GIP testing for bacteria, virus and parasite testing may be indicated, and thus a Medicare benefit.

Satisfaction – Additional Improvements

• Ordering Practices
  ▪ By site & Provider Type

• Reporting Results
  ▪ Blind results for C. diff on patients <2 yo
  ▪ Perform Toxin Screen on all positive C. diff results (2-step)
  ▪ Autoverification of negatives

• Guidelines/Algorithms
  ▪ Multidisciplinary team developed “best practice guideline”
  ▪ Adapted from available references to be customized to our orderables
  ▪ Notify ordering users of available guideline

• Ordering Enhancements
  ▪ Embed guideline hyperlink in orderable
  ▪ Create links to guideline
  ▪ Create “alternative suggestions” during ordering process
  ▪ Apply to acute and ambulatory order sets
**Recommendations**

The interpretation of 2-step testing is as follows:

- A negative PCR test excludes the diagnosis, no treatment is needed.
- A positive PCR followed by a positive toxin test will confirm the diagnosis of active C. difficile disease, and treatment is needed.
- A positive PCR followed by a negative toxin test will indicate colonization, and treatment is not needed. Colonized inpatients will still need to be isolated in the hospital.
How does your lab perform C. diff testing?

Panel Question

• A – NAAT only
• B – NAAT followed by Ag/Toxin Screen
• C – Ag/Toxin screen followed by NAAT
• D – Toxigenic Culture
• E – Other
**Laboratory Testing for Infectious Causes of Diarrhea**

- **Community-acquired diarrhea ≥ 7 days duration**
  - OR
  - **Travel-related diarrhea**
  - OR
  - **Diarrhea with risk factors for severe disease**

- **Health care-associated diarrhea (onset after 3rd inpatient day) or recent antibiotic use**
  - No
  - Yes
    - **Clostridium difficile by PCR**
      - *87493.01*
      - Positive
        - **Clostridium difficile Toxin Screen**
          - *LAB 1416*
        - Negative
          - **Use clinical judgment to guide need for additional testing**

- **Gastrointestinal PCR Panel**
  - *87045.08*
  - Positive
    - **No additional testing required**
  - Negative
    - **If diarrhea persists:**
      - **Consider Send-Outs**
        - Cyclospora Stain *LAB 960*
        - Cryptosporidium Ag, Feces *LAB 2041*
        - Giardia Ag, Feces *LAB 2042*
        - Enteric Pathogens Culture *LAB 0180*

Notes:
1. Risk factors for severe disease include age, immunocompromised state, bloody diarrhea, dehydration, fever, current or need for hospitalization, and severe abdominal pain.
2. Detection via molecular methods does not differentiate between viable and non-viable/treated organism; therefore, positive results can persist > 30 days after treatment.
3. Panel detects: Adenovirus, Astrovirus, Campylobacter spp., Clostridium difficile, Cryptosporidium, Cyclospora cayetanensis, Entamoeba histolytica, Enterovirulent E. coli (EAEC), Enteropathogenic E. coli (EPEC), Enteroaggregative E. coli (EIEC), E. coli O157, Shiga-like toxin-producing E. coli (STEC), Shigella/ Enteroinvasive E. coli (EIEC), Giardia lamblia, Norovirus, Plesiomonas shigelloides, Rotavirus, Salmonella spp., Sapovirus, Vibrio parahaemolyticus, Vibrio vulnificus, Vibrio cholera, and Yersinia enterocolitica.
4. Send-outs to a reference lab may require ≥ 72 hours before results are available.
5. Positive Toxin Screen indicates active disease. Negative Toxin Screen is usually not included.
Ordering Enhancements

**After the Change:**
The original order displays optional procedures and relative cost information. The appropriate procedure(s) can be selected. An Algorithm Link to best practice guidelines also displays.

<table>
<thead>
<tr>
<th>GI Pathogen Tests</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal PCR Panel testing is only indicated for patients in certain situations. Please refer to the testing algorithm to help determine the appropriate order by clicking on the link below.</td>
<td></td>
</tr>
<tr>
<td>GI Algorithm Link</td>
<td></td>
</tr>
<tr>
<td>☐ Cyclospora Stain $</td>
<td></td>
</tr>
<tr>
<td>☐ Cryptosporidium Antigen, Feces $</td>
<td></td>
</tr>
<tr>
<td>☐ Giardia Antigen, Feces $</td>
<td></td>
</tr>
<tr>
<td>☐ Clostridium difficile by PCR $</td>
<td></td>
</tr>
<tr>
<td>☐ Enteric Pathogens Culture, Stool $$</td>
<td></td>
</tr>
<tr>
<td>☐ Gastrointestinal PCR Panel $$$$</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Pathogen Tests</th>
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<td>Respiratory PCR Panel testing is only indicated for patients in certain situations. Please refer to the testing algorithm to help determine the appropriate order by clicking on the link below.</td>
<td></td>
</tr>
<tr>
<td>Respiratory Algorithm Link</td>
<td></td>
</tr>
<tr>
<td>☐ Influenza A&amp;B by PCR $$</td>
<td></td>
</tr>
<tr>
<td>☐ RSV by PCR $$</td>
<td></td>
</tr>
<tr>
<td>☐ RSV &amp; Influenza by PCR $$$</td>
<td></td>
</tr>
<tr>
<td>☐ Respiratory PCR Panel $$$$</td>
<td></td>
</tr>
</tbody>
</table>
ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults – Riddle et al.
### COST NOT NEUTRAL

<table>
<thead>
<tr>
<th></th>
<th>1,948-GI PCR</th>
<th>1,948 - Combo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of Goods Sold</td>
<td>$ 318,233.33</td>
<td>$ 226,787.78</td>
</tr>
<tr>
<td>Labor</td>
<td>$ 7,187.73</td>
<td>$ 64,690.87</td>
</tr>
<tr>
<td>Supplies</td>
<td>$ 301,940.00</td>
<td>$ 158,119.16</td>
</tr>
<tr>
<td>Contract/Maint</td>
<td>$ 8,034.60</td>
<td>$ 2,835.00</td>
</tr>
<tr>
<td>Depreciation</td>
<td>$ 1,071.00</td>
<td>$ 1,142.75</td>
</tr>
</tbody>
</table>

| Cost per Test        | $ 163.36      | $ 116.42      |

Labor rate 1 min = 0.73797
Labor rate 5 min = 3.6898
Labor rate 1 hr = 44.278493
GENERAL ASSUMPTIONS

• COMPARITIVELY EXPIDITIOUS
  - Equal processing time
  - Less manual interpretation time
  - Less clerical time
  - Faster Turn-Around-Time (TAT)

• IMPROVED DETECTION
• IMPROVED PATIENT OUTCOMES
• PHYSICIAN & PATIENT SATISFIER
• COST NEUTRAL

REALIZATIONS

• EXPIDITIOUS
  - Clerical time about the same

• IMPROVED PATIENT OUTCOMES
  - Mixed results

• SATISFIER
  - Mixed results

• COST NEUTRAL
  - Supply expense increased
Panel Discussion

Allen Bateman, PhD
Eric Beck, PhD
Blake Buchan, PhD
Tyler Radke, MLS(ASCP)
Tyler Tschanz, CLS(ASCP)
Does your lab run a molecular GI panel that has *Vibrio cholerae* on it?

Panel Question

- A – Yes
- B – No
For labs running *Vibrio cholerae*, how do you treat positive specs?

<table>
<thead>
<tr>
<th>Panel Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>A – Report positive, send to WSLH</td>
</tr>
<tr>
<td>B – Report as positive PCR w/ culture confirmation to follow (either in house or at WSLH).</td>
</tr>
<tr>
<td>C – Mask the result (don’t report) until culture performed for confirmation. Report culture result.</td>
</tr>
<tr>
<td>D – Mask the result (don’t report) and don’t do anything else.</td>
</tr>
<tr>
<td>E – Other</td>
</tr>
</tbody>
</table>
How does your lab handle positive C. diff on Multiplex panels?

Panel Question

- A – No additional testing
- B – Chart validation
- C – Reflex additional testing
- D – Leave for next shift
- E – Other
How do you gain approval of a new multiplex assay?

Panel Question

- A – Bring to Pathology Committee
- B – Bring to AMS Committee
- C – Bring to Value Analysis
- D – Bring to Laboratory Stewardship
- E – Other
Panel Questions

- Is it time to bring back Stool Culture?
- How do you handle overutilization?
- Are providers asking for lower cost options?
- Do you have population exclusions for testing?
- What size multiplex panel are you using or interested in?
- Added cost improving care or just detections?
Thank You!
If additional time, review of study from Allen Bateman, PhD
Clinical Infectious Diseases

Clinical impact of a Multiplex Gastrointestinal PCR Panel in Patients with Acute Gastroenteritis

Robert J Cybulski, Jr, Allen C Bateman, Lori Bourassa, Andrew Bryan, Barb Beail, Jason Matsumoto, Brad T Cookson, Ferric C Fang

Clinical Infectious Diseases, ciy357, https://doi.org/10.1093/cid/ciy357

Published: 25 April 2018   Article history ▼
Objectives

Assess the clinical relevance and utility of BioFire FilmArray GI panel

1. Determine whether patients detected by multiplex PCR have comparable clinical features to those diagnosed with conventional methods
   - Clinical features of patients positive by
     - FilmArray and stool culture (concordant) vs
     - FilmArray only (discordant)

2. Measure the impact of more rapid diagnosis on clinical decision-making and therapy
   - Compare to stool culture
     - Sensitivity
     - TAT
     - Antimicrobial treatment
     - Initiation, empiric vs targeted, discontinuation
Study design

- Parallel testing
  - Jan 1 – Sep 30, 2017
- Historical control, stool culture
  - Jan 1 – Sep 30, 2016
- Eligible subjects
  - Outpatients
  - Newly-admitted (<3d) inpatients
  - From 17 outpatient clinics, UWMC, and HMC

1,887 stool specimens

Stool culture
- *Salmonella*
- *Shigella*
- *Campylobacter*
- *E. coli* O157:H7
- *Yersinia*
- *Vibrio*
- *Aeromonas*
- *Plesiomonas*

FilmArray™ Gastrointestinal Panel

1 Test. 22 Targets. All in about an hour.

- Bacteria
- Parasites
- Viruses

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Parasites</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter (anaerobic)</td>
<td>Cryptosporidium</td>
<td>Adenovirus F, 40/41</td>
</tr>
<tr>
<td><em>Salmonella</em></td>
<td>Cyclospora cayetanensis</td>
<td>Astrovirus A</td>
</tr>
<tr>
<td>Yersinia: <em>Shigella</em></td>
<td>Enterotoxigenic <em>E. coli</em> (ETEC)</td>
<td>Rotavirus A</td>
</tr>
<tr>
<td><em>Vibrio</em></td>
<td>Enteropathogenic <em>E. coli</em> (ETEC)</td>
<td>Shigella (I, II, IV and V)</td>
</tr>
<tr>
<td><em>Aeromonas</em></td>
<td>Enteropathogenic <em>E. coli</em> (ETEC)</td>
<td>Shigella (I, II, IV and V)</td>
</tr>
<tr>
<td><em>Plesiomonas</em></td>
<td>Enterotoxigenic <em>E. coli</em> (ETEC)</td>
<td>Shigella (I, II, IV and V)</td>
</tr>
</tbody>
</table>
Testing and reporting

• Stool culture orderable replaced with ‘Enteric Pathogens by PCR’ test (Jan 1, 2017)

• Clinicians informed
  – in-person presentations
  – institution-wide memorandum from medical directors

• Stool in Cary-Blair medium, FilmArray GI tested/reported on receipt
  – 11pm-7am, tested/reported following morning

• Stool culture results not reported

• Parasite and virus tests performed as ordered
  – O&P, modified acid-fast smear, Giardia antigen, LDT viral PCR

• Results reported in LIS
  – STEC, called to clinicians
Chart review

- Chart review on all stool culture positives and FilmArray™ positives (n=579)
  - Demographics
  - Signs and symptoms of gastroenteritis
  - Antimicrobial treatment

- Times obtained from LIS
  - Sample collection
  - Arrival in lab
  - Result reported

- Empiric therapy = therapy initiated prior to the release of results
- Targeted therapy = therapy initiated after results released AND clinician prescribed agent with predicted activity against microbe detected
Pathogen Detection

**Detected by Conventional Stool Culture**
- Total: 103

**Detected by FilmArray**
- Total: 912

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Conventional Stool Culture</th>
<th>FilmArray</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aeromonas spp.</strong></td>
<td>8</td>
<td>0.4</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Campylobacter spp.</strong></td>
<td>51</td>
<td>2.7</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Plesiomonas shigelloides</strong></td>
<td>0</td>
<td>0.0</td>
<td>0.0142</td>
</tr>
<tr>
<td><strong>Salmonella spp.</strong></td>
<td>13</td>
<td>0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Shigella/EIEC</strong></td>
<td>28</td>
<td>1.4</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Vibrio spp.</strong></td>
<td>4</td>
<td>0.2</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Yersinia spp.</strong></td>
<td>7</td>
<td>0.4</td>
<td>0.0414</td>
</tr>
<tr>
<td><strong>E. coli O157:H7</strong></td>
<td>3</td>
<td>0.2</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Shiga-like toxin producing E. coli</strong></td>
<td>21</td>
<td>1.1</td>
<td>0.0002</td>
</tr>
</tbody>
</table>
Clinical Features

- Patients with classic enteric bacterial pathogens by FilmArray
- Concordant = identified by FilmArray and stool culture
- Discordant = identified by FilmArray only
- Patients with concordant results: nonsignificant trend toward greater symptom severity
- Patients with discordant results: longer symptom duration
### Turnaround time and clinical decision-making

<table>
<thead>
<tr>
<th></th>
<th>2016 Culture</th>
<th>2017 FilmArray™</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases Reviewed, n</td>
<td>83</td>
<td>496</td>
<td>n/a</td>
</tr>
<tr>
<td>Median Time Collection to First Report (h)</td>
<td>47.0</td>
<td>18.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with bacteria/parasite identified, n</td>
<td>83</td>
<td>420</td>
<td>n/a</td>
</tr>
<tr>
<td>Eligible patients prescribed antimicrobials, n (%)</td>
<td>50 (60.3)</td>
<td>272 (63.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Empirical antimicrobial prescription, n (%)</td>
<td>20 (40.0)</td>
<td>64 (23.5)</td>
<td>0.0148</td>
</tr>
<tr>
<td>Median Time Collection to Antimicrobial (h)</td>
<td>72.0</td>
<td>26.0</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Turnaround time and clinical decision-making

Initiation of Antimicrobial Therapy, 2016

Number of Patients, n

Targeted Therapy
Empiric Therapy

Time to Result (h)

1-10 11-20 21-30 31-40 41-50 51-60 61-70 71-80 81-90 91-100

Initiation of Antimicrobial Therapy, 2017

Number of Patients, n

Targeted Therapy
Empiric Therapy

Time to Result (h)

1-10 11-20 21-30 31-40 41-50 51-60 61-70 71-80 81-90 91-100
Turnaround time and clinical decision-making

Targeted versus Empirical Therapy by Month, 2017

Number of Patients, n

- Targeted Therapy
- Empirical Therapy

Month

January, February, March, April, May, June, July, August, September
STEC infections

- 9 of 21 patients with STEC empirically prescribed ABX
- 8 of 9 cases, discontinued after STEC reported
  - Median of 8h from results to discontinuation

### STEC identified

<table>
<thead>
<tr>
<th>Method</th>
<th># STEC identified</th>
<th>TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FilmArray</td>
<td>21 (4 O157:H7)</td>
<td>18h</td>
</tr>
<tr>
<td>Stool culture + Shiga toxin immunoassay</td>
<td>3 O157:H7</td>
<td>60h (positive)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75h (negative)</td>
</tr>
</tbody>
</table>
Pathogen Detection

Improved Detection by FilmArray™ Compared to Conventional Testing

- Classic Enteric Bacterial Pathogens (Culture)
- Multiplex Viral Pathogen PCR
- Entamoeba histolytica and Giardia lamblia (O&P)
- Giardia lamblia (Antigen Test)
- Cryptosporidium or Cyclospora (Modified Acid Fast Stain)

Legend:
- Blue: Concordant Detection: Positive by FilmArray™ and Conventional
- Pink: Enhanced Detection: Positive by FilmArray™, False Negative by Conventional
- Orange: Additional Detection: Positive by FilmArray™, Conventional not Ordered