The Scoop on Poop II

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Disclosures

- **Research Funds**
  - Luminex
  - Biofire
  - BD

- **Advisory**
  - Luminex
  - Biofire
  - BD
  - Hologic

Courtesy of B. Robinson-Dunn
Objectives

- Review of the following:
  - Epidemiology of GI illness in US
  - Clinical Presentation and Workup of GI illness
  - Traditional Clinical Laboratory Procedures
  - FDA-cleared Multiplex panels
  - The Advantages/Concerns of GI multiplex panels
  - The impact for public health
Multiple Sources of Exposure
Multiple and Similar/Overlapping Symptoms

K. Chapin MD
Traditional Testing Requires Multiple Diagnostics
211-375 million episodes of diarrheal illness occur in the United States each year, resulting in:

- 73,000,000 physician visits
- 323,000 - 1,800,000 hospitalizations
- 3,100-5000 deaths
- $6 billion spent on medical care and lost productivity

World-wide diarrhea approx 1.7 billion

What are the Issues in Diagnosis of Acute Gastrointestinal Illness?

- Symptoms of different organisms causing gastrointestinal illness overlap
  - Unclear what pathogen the patient is infected with and what tests to request
  - Treating **empirically**, **antibiotics** +/- hydration, maybe stool studies

- Current traditional test methods are not comprehensive enough in menu, not sensitive enough or rapid enough to have a clinical impact
  - Last summer’s Shigella outbreak 40% of patients were not detected by culture

- No sample to test
  - Patient may not be able to provide a specimen at the time of visit, rarely return a specimen if asked to collect at home

- High costs with little benefit for the patient
  - 1-10 tests ordered per acute gastrointestinal patient seen
  - Over 60% with no diagnosis
# Chart Common GI Pathogens/Toxins – Signs and Symptoms

K. Chapin MD 2015

<table>
<thead>
<tr>
<th>Organism</th>
<th>Pathogen</th>
<th>Onset</th>
<th>Fever</th>
<th>Nausea</th>
<th>Abd Pain</th>
<th>Vomiting</th>
<th>Diarrhea watery</th>
<th>Diarrhea bloody</th>
<th>Significant Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Campylobacter</td>
<td>2-5 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Guillain-Barré, IBS</td>
</tr>
<tr>
<td></td>
<td>Salmonella</td>
<td>12h-3 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>HA, extraintestinal disease, SS</td>
</tr>
<tr>
<td></td>
<td>Shigella</td>
<td>1-4 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Mucus and WBC, life threatening</td>
</tr>
<tr>
<td>Virus</td>
<td>Norovirus</td>
<td>1-3 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Rotavirus</td>
<td>1-3 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>&lt; 2, elderly severe dehydration</td>
</tr>
<tr>
<td>Toxin</td>
<td>C difficile toxin</td>
<td>Days-mos</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Nosocomial, chronic</td>
</tr>
<tr>
<td></td>
<td>E.coli shiga toxins</td>
<td>2-10 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>HUS</td>
</tr>
<tr>
<td></td>
<td>ETEC</td>
<td>12h-5days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Traveler's diarrhea</td>
</tr>
<tr>
<td>Parasite</td>
<td>Giardia</td>
<td>3-25 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Chronic, Malabsorption</td>
</tr>
<tr>
<td></td>
<td>Cryptosporidium</td>
<td>2-7 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Immunocomp debilitating</td>
</tr>
</tbody>
</table>

Common to all: diarrhea, dehydration, anorexia, period of shedding, variety of reservoirs


Manual of Communicable Diseases CDC 2013
Standard Menu of Infectious GI Pathogens Assessed at Lifespan

- Nine pathogens available
- Bacterial
  - Salmonella
  - Shigella
  - Campylobacter
- Toxin Production
  - E. coli O157 (shiga-toxin only)
  - C. difficile ToxinA/B
- Viral
  - Rotavirus
  - Adenovirus
- Parasitic screen
  - Giardia/Cryptosporidium
- Send out
  - Full Ova and Parasite,
  - Norovirus
  - Cyclospora (acid fast stain)
  - Shiga toxins other than 0157

What am I missing? Maybe this is just a virus? Traveler’s diarrhea? Do I know for sure? Does it matter if I know or if the patient knows?
Come check out our stool samples.
Traditional Testing Requires Multiple Diagnostics

Confusion, inefficiency and duplication of processes
The “Cloud” of Stool Testing Methods

Specimen comes to lab

Order entry and correction of order

Send out requests
- Noro PCR
- O and P
- Acid Fast smear

C difficile toxin PCR

Inoculating to culture plates and division of specimen to other lab sections

Culture Plates incubated and then to reading bench

Sub Isolate and/or Send Reportable to DOH

• Virology Shell culture
• Rotovirus EIA
• DFA confirmatory Giardia/Crypto

Giardia/Crypto EIA (O and P Screen)

Send out requests

The “Cloud” of Stool Testing Methods
### A Comparison of Current Diagnostic Methods

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Stool Culture</th>
<th>O&amp;P Staining</th>
<th>EIA</th>
<th>DFA</th>
<th>Traditional PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to Result</strong></td>
<td>2–5 days</td>
<td>10 days to 2 weeks</td>
<td>&lt;1-2 hours</td>
<td>3 hours to 2 days</td>
<td>5–6 hours</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>77%–91%</td>
<td>50%–90%</td>
<td>75%–95%</td>
<td>90%–99%</td>
<td>up to 100%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>61%–78%</td>
<td>80%–90%</td>
<td>83%–98%</td>
<td>95%–100%</td>
<td>up to 100%</td>
</tr>
</tbody>
</table>

DFA=direct fluorescent antibody; EIA=enzyme immunoassay; O&P=ova and parasite; PCR=polymerase chain reaction.
### Annual Costs and Reimbursement (2013)

<table>
<thead>
<tr>
<th>Stool Testing</th>
<th>reagent cost/test</th>
<th>Tech time</th>
<th># days</th>
<th>Total time</th>
<th>Tech cost</th>
<th>Total cost/test</th>
<th>Medicare Reimbursement</th>
<th>Lifespan Lab Charge</th>
<th># stools</th>
<th>Total cost</th>
<th>Total Medicare Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool negative</td>
<td>$8.40</td>
<td>20 min</td>
<td>2</td>
<td>20 min</td>
<td>$13.40</td>
<td>$284,965</td>
<td>$12.36</td>
<td>$175.27</td>
<td>3304</td>
<td>$44,273.60</td>
<td>$40,837.44</td>
</tr>
<tr>
<td>E. coli 0157 toxin</td>
<td>250,000 to 500,000 costs</td>
<td>molecular with 2-2.5 million reimbursement</td>
<td>no separate service code, very low num</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool positive (33%)</td>
<td>$33.40</td>
<td>20 min</td>
<td>4</td>
<td>80 min</td>
<td>$57.40</td>
<td>$176.27</td>
<td>1627</td>
<td>$93,389.80</td>
<td>$20,109.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool culture total</td>
<td>4931</td>
<td>$137,663.40</td>
<td>$60,947.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasite screen</td>
<td>$6.00</td>
<td>10 min</td>
<td>10 min</td>
<td>$10.20</td>
<td>$33.98</td>
<td>$85.69</td>
<td>3449</td>
<td>$35,179.80</td>
<td>$117,197.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rota virus</td>
<td>$9.00</td>
<td>10 min</td>
<td>10 min</td>
<td>$13.20</td>
<td>$16.99</td>
<td>$130.00</td>
<td>201</td>
<td>$2,653.20</td>
<td>$3,414.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noro virus: reagent pricing based on HSV PCR</td>
<td>$28.50</td>
<td>2 hours</td>
<td>1</td>
<td>2 hours</td>
<td>$50.00</td>
<td>$78.50</td>
<td>$49.71</td>
<td>$127.35</td>
<td>not routinely sent out</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiga toxin panel</td>
<td>$18.00</td>
<td>10 min</td>
<td>10 min</td>
<td>$22.20</td>
<td>$16.99</td>
<td>$109,468.20</td>
<td>4931</td>
<td>$83,777.69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O and P c diff</td>
<td>$14.00</td>
<td>send out</td>
<td>n/a as this will still need to be sent out if the GPP is negative</td>
<td>425</td>
<td>Total annual cost: $284,965</td>
<td>$265,336.86</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$284,965 lab cost versus $265,337 reimbursement traditional methods

250,000 to 500,000 costs molecular with 2-2.5 million reimbursement

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11/17/2015
Figure 3. Range and median cost for traditional methods of detection

L.K. Clinton$^{1, 2}$, T. Enomoto$^2$, C. Ying$^2$, W. Kim$^2$, and M.J. Bankowski$^{1, 2}$

$^1$Department of Pathology, John A Burns School of Medicine, University of Hawaii, Honolulu, HI and $^2$Diagnostic Laboraory Services, Inc. (The Queen’s Medical Center), Aiea, HI
Clinical/Laboratory Overlap Considerations

- Patient issues
  - How easy or difficult do we make diagnosis of GI disease for the patient?
- Provider assessment
  - What do providers know?
  - What are their practices?
- Survey to providers
• What % of patients that enter your healthcare system with gastroenteritis get stool studies (not including \textit{C. difficile} toxin)?
  ○ 25, 50, 75, 100%
Provider Stats

- Only **25%** order stool studies on most patients presenting with gastroenteritis
  - Per month in the Pedi ER
    - 400 patients and < 100 specimens received in the lab
- Why?
  - GI guidelines selective approach don’t recommend routine testing
  - Patient could not provide a specimen
  - TAT is not particularly clinically useful
  - Empiric antibiotics recommended in some guidelines
    - Cipro and Metronidazole
Patient Issues

• What % of patients return specimen containers for stool testing when sent home with them?
  ○ 5%, 25%, 50%, 75%, 100%, DNK

• DNK for sure but assumed less than 5% return a specimen to the lab as determined by the head of the Pedi ER
Overwhelmed Patient....
Baggie of Vials, Toilet Hat, 10-step Directions

- Directions the patient has a hard time interpreting
- Asked to collect and SCOOP multiple samples and store in the refrigerator
- Return of specimens to a lab
Comparison of FecalSwab and ESwab Devices for Storage and Transportation of Diarrheagenic Bacteria

Jari J. Hirvonen* and Suvi-Sirkku Kaukoranta

FecalSwab™ Screw Cap Tube 12 X 80mm with 2ml Modified Cary-Blair Medium, 1 Regular Flocked Swab

- The FecalSwab proved to be suitable even for extended storage and transportation of enteric pathogens, enabling successful and reliable microbiological analysis when specimens are sent to either a local laboratory or a more distant reference laboratory
- Easier for analysis on automated platforms
- *Easier for use with multiplex platforms potentially
  - not FDA cleared for use with any molecular platform at this time
- *UNMET clinical need.....patient here in front of me I want to get a sample
Provider Testing Knowledge

- **60%** of physicians did not know what was included in a routine bacterial stool culture
  - Salmonella, Shigella, Campylobacter
- **70%** did not know rejection criteria of a specimen
  - RT clean vial 4 hours would be rejected

**Bottom line**
- We are making a lot of assumptions on stool pathogen data that are probably inaccurate
- Lab needs to help providers understand pre-analytical, analytical and *post-analytical components* esp. in the era of multiplex
- **Maybe** using one vial, one test, more flexibility on collection and transport requirements will make detection of GI illness easier or better?
Synopsis : Current Diagnostic Methods

- Limitations associated with current testing methods:

  Lab Focus....
  - Time-consuming
  - Labor-intensive
  - Technically complex / require specific expertise
  - Lack sensitivity and specificity

  Provider Focus....
  - Limited coverage of current test options and often don’t get an answer?
  - Overlapping symptoms
  - Need to order multiple tests specific for suspected organisms
  - Tests for many organisms are not available or unsure how to order

Net effect: Low yield, High cost, inefficiency, duplication, confusion

New Technology: Multiplex Tests for GI Pathogens
Lab Process - Strategy for Evaluation

- New technology / Needs assessment clinically
- Validation (LDT) versus verification (FDA-cleared)
  - Taken us over 2 years to evaluate a number of GI Multiplex methods
  - Looking at other specimen collection types, input, added organisms
- Design / perform evaluation
- Consider:
  - Budget plan, Return on investment (ROI), integration with other equipment
  - Lab training, workflow (batch, single use), vendor support
  - EMR issues
  - Education to providers and end users
  - Public Health Implications
- Implementation
- Review post-implementation
  - Objectives to measure outcome
  - Address cost-avoidance, improved patient outcome
## Total GI Pathogen Request/Year Lifespan (2013)

<table>
<thead>
<tr>
<th>Test Request</th>
<th>Inpatient</th>
<th>Outpatient</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool Culture</td>
<td>1355</td>
<td>3576*(70%)</td>
<td>4931</td>
</tr>
<tr>
<td>Rotavirus EIA</td>
<td>85</td>
<td>116</td>
<td>201</td>
</tr>
<tr>
<td>Crypto/Giardia EIA</td>
<td>606</td>
<td>2843*(82%)</td>
<td>3449</td>
</tr>
<tr>
<td>Adenovirus EIA</td>
<td></td>
<td></td>
<td>120</td>
</tr>
<tr>
<td>C. difficile toxin</td>
<td>8110*(67%)</td>
<td>3890</td>
<td>12701*(62%)</td>
</tr>
</tbody>
</table>

* Most stool bacterial and parasites requests are **outpatient**
* Most C. difficile toxin requests are for **inpatients**
* C. difficile toxin requests makes up more than ½ of test requests

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No norovirus, Few Shiga toxin

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What Multiplex Test Do I Pick? Kid in a candy store...
# Current FDA-cleared GI Multiplex Panels

<table>
<thead>
<tr>
<th>BACTERIA</th>
<th>Biofire</th>
<th>Luminex</th>
<th>Hologic</th>
<th>BD*</th>
<th>Nanosphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Salmonella</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Shigella/Enteroinvasive E. coli (EIEC)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Shiga-like toxin-prod. E. coli (STEC)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clostridium difficile (Toxin A/B)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli O157</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic E. coli (ETEC) LT/ST</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aeromonas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteroaggregative E. coli (EAEC)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vibrio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Enteropathogenic E. coli (EPEC)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Plesiomonas shigelloides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

| VIRUS                                         |         |         |         |     |            |
| Norovirus group GI/II                         |         |         |         |     | X          |
| Rotavirus A                                   |         |         |         |     | X          |
| Adenovirus F40/41                             |         |         |         |     | X          |
| Astrovirus                                    |         |         |         |     |            |
| Sapovirus                                     |         |         |         |     |            |

| PROTOZOA                                      |         |         |         |     |            |
| Giardia lamblia                               | X       | X       |         |     | X          |
| Cryptosporidium                               | X       | X       |         |     | X          |
| Entamoeba histolytica                         | X       | X       |         |     | X          |
| Cyclospora cayetanensis                       |         |         |         |     | X          |

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Table of Positive Stool Pathogens

Culture/Routine Testing vs Molecular Diagnostic Panels

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Culture/Routine Test (Lifespan)</th>
<th>BD MAX™ Enteric Bacterial Panel</th>
<th>xTAG® GPP - Luminex</th>
<th>FilmArray™ GI Panel - Biofire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sapovirus</td>
<td>3.9% (14)</td>
<td>3.0% (11)</td>
<td>0.5% (2)</td>
<td>0.8% (3)</td>
</tr>
<tr>
<td>Norovirus</td>
<td>3.0% (11)</td>
<td>0.5% (2)</td>
<td>1.1% (4)</td>
<td>1.4% (5)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>0.8% (3)</td>
<td>1.1% (3)</td>
<td>1.1% (3)</td>
<td>0.8% (3)</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>7.5% (27)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteroaggregative E. coli (EAEC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteropathogenic E. coli (EPEC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiga-like toxin-producing E. coli (STEC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic E. coli (ETEC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigella/Enteroinvasive E. coli (EIEC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Results represent number of true positive (TP) pathogens. TP were those that resulted positive on 2/3 methods or after discrepant analysis.

K. Chapin MD 11/17/2015

30
Comparison of Methods for Detection of True Positive Pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Biofire</th>
<th>Magpix</th>
<th>BD MAX</th>
<th>Clinical Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campy</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Shig</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Salm</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>STEC</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ETEC</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rota</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noro</td>
<td>11</td>
<td>10</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Giard</td>
<td>4</td>
<td>4</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>EC</td>
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out of 361
<table>
<thead>
<tr>
<th>Biofire Results</th>
<th>Magpix Results</th>
<th>BD MAX Results</th>
<th>Clinical Lab Result (if available)</th>
<th>Discrepant Determination</th>
<th>Final Determination</th>
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<td>Cryptosporidium</td>
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<td>FP crypto BF</td>
<td>TN^1</td>
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<td>ETEC, Noro</td>
<td>Noro</td>
<td>N/A</td>
<td>not ordered</td>
<td>FP ETEC BF</td>
<td>TP^1</td>
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<td>N/A</td>
<td>not ordered</td>
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<td>FP Campy</td>
<td>FN Campy MP</td>
<td>TP^1</td>
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<td>Salmonella</td>
<td>Salmonella</td>
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<td>TN^1</td>
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<td>Negative</td>
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<td>Negative</td>
<td>FP Campy</td>
<td>TN^1</td>
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<tr>
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<td>Negative</td>
<td>Negative</td>
<td>FP Campy</td>
<td>TN^1</td>
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<tr>
<td>Noro, Campy</td>
<td>Negative</td>
<td>Negative</td>
<td>neg Campy, Noro not ordered</td>
<td>FP Campy &amp; Noro BF</td>
<td>TN^1</td>
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<tr>
<td>Noro</td>
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<td>not ordered</td>
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<td>TN^1</td>
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</tr>
<tr>
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<td>N/A</td>
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</tr>
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<td>N/A</td>
<td>FN ETEC MP</td>
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<td>neg Giardia, Noro not ordered</td>
<td>FN ETEC MP</td>
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<tr>
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<tr>
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<td>Crypto (&amp; IC failed)</td>
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<td>not ordered</td>
<td>FP Crypto MP</td>
<td>TN^1</td>
</tr>
<tr>
<td>Negative</td>
<td>Noro</td>
<td>N/A</td>
<td>not ordered</td>
<td>FP Noro MP</td>
<td>TN^1</td>
</tr>
<tr>
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<td>TN^1</td>
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<td>TN^1</td>
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<td>N/A</td>
<td>not ordered</td>
<td>FN Noro MP</td>
<td>TP^1</td>
</tr>
<tr>
<td>Negative</td>
<td>Salmonella</td>
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<td>Negative</td>
<td>FP Salmon MP</td>
<td>TN^1</td>
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<td>TN^1</td>
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<td>E. coli O157</td>
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<td>TN^1</td>
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<td>E. coli O157, Giardia</td>
<td>Negative</td>
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<tr>
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<td>Giardia</td>
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<td>Salmonella</td>
<td>neg Giardia</td>
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</tr>
<tr>
<td>Negative</td>
<td>Giardia</td>
<td>Salmonella</td>
<td>neg Giardia</td>
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<td>BD MAX</td>
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<td>Negative</td>
<td>Salmonella</td>
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<td>FP Salmon MP</td>
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</tr>
<tr>
<td>Negative</td>
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<td>Salmonella</td>
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<td>TN^1</td>
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<td>Shigella</td>
<td>Shigella</td>
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<td>Campy</td>
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<td>Campy</td>
<td>Negative</td>
<td>Campy</td>
<td>FN Campy MP</td>
<td>TN^1</td>
</tr>
</tbody>
</table>
Discrepant analysis:
- Many samples were falsely negative by culture or Shiga toxin EIA.
- Positive by alternate PCR
  - 22/51 (43.1%) for *Campylobacter* spp.
  - 19/26 (73.1%) for *Salmonella* spp.
  - 9/10 (90%) for *Shigella* spp.
  - 9/17 (52.9%) for Shiga toxins
Three multiplex molecular enteric panels (BD MAX™, BioFire FilmArray®, and Verigene®)

126 samples and not all 3 methods evaluated
- Good agreement for all molecular methods
- False positive results with the EIA methods in use, this study indicates it was as high as 75% for Campylobacter
Multiplex Detection of Gastrointestinal Pathogens: A Comparative Evaluation of Two Commercial Panels Using Clinical Stool Specimens

Reeti Khare et al, JCM 2014

- 230 prospectively collected samples, routine testing GI pathogens in 19 (8.3%) samples, compared to 76 (28.3%) by the FilmArray and 69 (20%) by Luminex assay
- **Norovirus, C. diff toxin and Sapo virus** most common pathogens identified
- There was an average of **3 routine tests** ordered per sample using traditional test methods
Interpretation: Co-infection and carriage rates

Sapovirus - tastes like breast milk
Shigella - tastes like applesauce
GI Pathogen Detection

Figure 1  A. Detection of GI pathogens with culture vs FA-GI.  B. Patient age demographics

Figure 2  A. Categories of GI pathogens detected. B. GI pathogens detected as co-infections.

L.K. Clinton¹, ², T. Enomoto², C. Ying², W. Kim², and M.J. Bankowskii¹, ²
¹Department of Pathology, John A Burns School of Medicine, University of Hawaii, Honolulu, HI and ²Diagnostic Laboratory Services, Inc. (The Queen’s Medical Center), Aiea, HI
### TABLE 3 Total number of FilmArray GI Panel-positive specimens by number of detections

<table>
<thead>
<tr>
<th>No. of potential pathogens in FilmArray GI Panel result</th>
<th>No. of specimens (n = 1,556)</th>
<th>% of total (%) positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected (at least one)</td>
<td>832</td>
<td>53.47 (100)</td>
</tr>
<tr>
<td>One</td>
<td>570</td>
<td>36.63 (68.51)</td>
</tr>
<tr>
<td>Two</td>
<td>199</td>
<td>12.79 (23.92)</td>
</tr>
<tr>
<td>Three</td>
<td>50</td>
<td>3.21 (6.01)</td>
</tr>
<tr>
<td>Four</td>
<td>9</td>
<td>0.58 (1.08)</td>
</tr>
<tr>
<td>Five</td>
<td>3</td>
<td>0.19 (0.36)</td>
</tr>
<tr>
<td>Six</td>
<td>1</td>
<td>0.06 (0.12)</td>
</tr>
</tbody>
</table>
FilmArray and Luminex panels identified mixed infections in 21.1% and 13.0% of positive prospective samples, respectively.

Compared to 8.3% by routine methods.
Interpretation totally clear.......stay tuned.....
Multiplex Methods...here to stay

- Multiplex methods:
  - Detect more pathogens
  - Detect more mixed infections
  - Current culture methods lack sensitivity

- Presence of multiple pathogens may be underestimated by current routine test

- Further investigation on the mechanisms of co-infection, the organisms associated with them and the impact on clinical outcomes will be an important area of future research

- Current EIA methods likely not specificity (Campy) and sensitivity (Shiga toxin)

- Patient benefits for use of GI multiplex still to be determined....
  - Some early data on LOS, decreased hospital costs, decreased lab costs
Changes in Causes of Acute Gastroenteritis in the United Kingdom Over 15 Years: Microbiologic Findings From 2 Prospective, Population-Based Studies of Infectious Intestinal Disease

Clarence C. Tam

- $152 billion which are enormous sums for preventable diseases
- The major change in pathogen distribution between IID1 and IID2 was a drop in Salmonella cases, indicating the success of European-wide interventions and, notably, an industry-led Salmonella control program in chickens in the United Kingdom.
- Majority of stool specimens submitted in both studies by cases were negative for pathogens included in our diagnostic panel.
- **New-generation sequencing techniques** though not yet adapted for widespread use afford immense opportunities to identify novel pathogens to close the diagnostic gap.
- Among the known pathogens, effective control of norovirus, rotavirus, and Campylobacter infections remains a high priority
Is the Juice worth the Squeeze?

- Therapeutic—Results can improve patient management decision making, thereby minimizing use of inappropriate or unnecessary drugs.
- Accuracy—Stool culture is less sensitive than molecular methods, with molecular testing detecting almost 3 times as many infections in the same set of samples.
- Public health—Results can trigger outbreak investigations.
- Diagnostic—Results can mitigate further downstream unnecessary testing.
- Psychological—Results can lead to earlier peace of mind for the patient and physician once the causative pathogen has been identified.
“Remember, ordering a diagnostic test is like picking your nose in public: you must first consider what you will do if you find something.”

Catherine D. DeAngelis, MD
Multiplex Benefit Analysis: Clinical
(Verigene Website)

- **Clinical Benefits** – *Potential*
  - Results can improve therapeutic patient management, minimizing use of inappropriate or unnecessary drugs

- **Diagnostic** - *Potential*
  - Results can mitigate further downstream unnecessary testing

- **Psychological** - *Potential*
  - A result can provide peace of mind for the patient and physician once the causative pathogen has been identified

- **Economic Benefits** - *Potential*
  - Lower cost from reduced use of inappropriate or unnecessary antimicrobial or antiviral drugs.
  - Potential reduction in length of stay and length of isolation for patients in the hospital.
  - Reduced cost of sample send-out to reference laboratories.
“Underinsurance”
Skimpy insurance seen as next health care issue
By RICARDO ALONSO-ZALDIVAR  Associated Press

- It's not the uninsured, but rather the problem of high out-of-pocket costs for people already covered.
- After paying premiums, many low- and middle-income patients still face high costs when trying to use their coverage.
- Countering... Network plans reduce deductibles, co-pays, out of pocket if you use their providers.
Reality of Patient Costs – Remember most Stool Testing is an OUTPATIENT test

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Assay</th>
<th>Medicare Reimbursement $</th>
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<tbody>
<tr>
<td>87493</td>
<td>C. diff PCR</td>
<td>47.76</td>
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<tr>
<td>87505</td>
<td>GI 3-5 targets</td>
<td>174.58</td>
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<tr>
<td>87506</td>
<td>GI 6-11 targets</td>
<td>290.45</td>
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<tr>
<td>87507</td>
<td>GI 12-25 targets</td>
<td>767.18</td>
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</tbody>
</table>
Affordable Care Act
Issue of “Underinsurance”

- Molecular reimburses more....
- But for outpatients charges will be passed to them in deductibles
- Provider and patient satisfaction at risk unless a true “value” and benefit is attached to the testing
Dr. Schreckenberger – point
Dr. McAdam – counterpoint

- Concept of patient satisfaction....patients having the ability to choose their provider
- Lifespan is very conscious about the patient’s satisfaction....
  - Providing Health with Care....
  - Healthcare is a business
90% thought *somewhat important* to provide an answer
80% thought *somewhat important* to get a single test result, more quickly, more inclusive
90% charge to patient was *somewhat important*
90% thought $125 - $250 was an appropriate charge for this test
IMPACT Study
Initiation of a multiplex GI Panel in Pediatrics

- Study looking at Pre and Post Implementation of a GI multiplex assay in pediatric ER setting
  - National Multi-site
- Purpose:
  - Will a rapid GI multiplex assay provide outcome benefits to the healthcare system
    - Reduced ER return calls or visits
    - Reduced antibiotics or more appropriate care
    - Increase provider and patient/parent satisfaction
    - Overall cost-avoidance for the system
    - Is a rectal swab collected at the time of the visit a useful specimen collection vs standard stool
- Supported by NIH and Biofire – Cost $2 million

K. Chapin MD 11/17/2015
Tennessee DOH
Burden 6/15/13 – 9/15/13

Isolates 81%
Culture 19%

21% Culture Independent Diagnostic Tests (CIDT)
EIA + broth 67%
Outbreak 12%

0%

Courtesy of AmyWoron
Nashville DOH
<table>
<thead>
<tr>
<th>Tennessee DOH</th>
</tr>
</thead>
</table>

### ISOLATES

- 479 correct / 492
- 97%

### Syndrome CIDT

- 14 correct / 24
- 58%

1. Are the CIDT results correct?  
2. Will the labs help DOH labs?

K. Chapin MD

11/17/2015
- Encourage labs to discuss with their DOH before implementation of Multiplex GI methods
- Come up with a mutually acceptable plan to provide isolates

Protocol for Specimen Processing for Submission of Bacterial GI Pathogens to DOH*

* State DOH requirements differ for isolate submission and pathogen/susceptibility reporting. The patient Cary-Blair specimen instead of isolates may also be acceptable. Check with your local DOH.

If Multiplex ID is:
- Salmonella
- Shigella
- Campy
- Shiga Toxins /0157
- Yersinia
- Vibrio
- Other Pathogens (e.g. Plesiomonas)

Sub Cary-Blair to:
- MAC and SS, HE, or XLD
- MAC and SS, HE, or XLD
- BAP and CAMPY
- GN/MAC Broth and Mac Sorbitol
- MAC and CIN
- MAC and TCBS
- MAC and GN broth

Send Isolate, GN/MAC broth or Cary-Blair to:
- Susceptibility Testing per lab protocol
- Department of Health

MAC = MacConkey agar
MAC Sorbitol = MacConkey agar with sorbitol
SS = salmonella-shigella agar
HE = Hektoen-enteric agar
XLD = Xylose-lysine-deoxycholate agar
BAP = Blood agar plate
CAMPY = Campylobacter medium
GN/MAC broth = Gram negative broth
CIN= Cefsulodin irgasan-novobiocin agar
TCBS= Thiosulfate-bile salt sucrose agar
Thanks to:
- Lindsay Leblanc
- Lynn Vickery
- Roberta Dickenson
- Vittal Ponraj
- The Micro Lab Staff