Advances in Gastrointestinal Pathogen Detection

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Children’s Health System,
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No Disclosures
Outline

1. Traditional methods of gastrointestinal pathogen detection

2. Molecular Platforms
   - Luminex xTAG Gastrointestinal Pathogen Panel
   - FilmArray Gastrointestinal Panel
   - Nanosphere Verigene Enteric Pathogen Panel

3. Benefits, limitations, and considerations
TRADITION METHODS OF GASTROINTESTINAL PATHOGEN DETECTION
Traditional stool culture
Traditional stool testing

In our lab...

**Bacteria**
- *Salmonella, Shigella, Campylobacter, Yersinia, E. coli 0157*
- *Aeromonas and Plesiomonas* (oxidase screen)

**Viruses**
- Rotavirus EIA
- Other testing is sent out

**Parasites**
- *Giardia & Cryptosporidium* immunoassay
- Other testing is sent out (including ova and parasite examination)
Limitations of traditional stool pathogen detection

• **Traditional bacterial culture**
  – 2 to 5 days for pathogen detection

• **Viral testing**
  – Many enteric viruses do no grow in viral culture
  – PCR detection of viruses is rapid, but only if testing is performed in house
  – Immunoassays can lack sensitivity

• **Ova and parasite examination**
  – Technically challenging requiring highly trained and experienced personnel
  – Time intensive
  – Detection is complicated by low organism burden and/or intermittent shedding
Traditional stool testing

• Slow turnaround time
• Labor intensive
• Can be technically challenging

• Require health care providers to select the appropriate test
  – many causes of diarrheal illness are clinically indistinguishable
Molecular Gastrointestinal Pathogen Detection

• Faster results
• Less hands on time
• Allows health care providers to cast a broad net when testing for infectious etiologies of gastroenteritis

What is available on the market...
MOLECULAR PLATFORMS
Luminex xTAG Gastrointestinal Pathogen Panel (GPP)
xTAG Gastrointestinal Pathogen Panel (GPP)

- Qualitative, bead-based assay
- Detects 14 bacterial, toxin, and viral, and parasitic GI pathogens
- Acceptable specimens
  - Raw fresh and frozen stool
  - Stool in Cary-Blair Transport Medium
- Initially FDA approved in 2012
  - 3 additional targets approved in 2014

www.luminexcorp.com
xTAG® GASTROINTESTINAL PATHOGEN PANEL

Workflow

Pre-PCR

Sample Pre-treatment
45-60 minutes

Nucleic Acid Extraction and Purification
45 minutes

Multiplex Application
2.5 hours

Post-PCR

Bead Hybridization and Detection
1 hour

Data Acquisition and Analysis by MAGPIX® or Luminex® 100/200™
10 minutes
## xTAG GPP Targets

<table>
<thead>
<tr>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial and Toxin</strong></td>
</tr>
<tr>
<td><em>Campylobacter</em> spp.¹</td>
</tr>
<tr>
<td><em>Clostridium difficile</em> Toxin A/B</td>
</tr>
<tr>
<td><em>Escherichia coli</em> 0157</td>
</tr>
<tr>
<td>Enterotoxigenic <em>E. coli</em> (ETEC) LT/ST</td>
</tr>
<tr>
<td>Shiga-like toxin producing <em>E. coli</em> (STEC) stx1/stx2</td>
</tr>
<tr>
<td><em>Salmonella</em> spp.</td>
</tr>
<tr>
<td><em>Shigella</em> spp.²</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
</tr>
<tr>
<td><strong>Viral</strong></td>
</tr>
<tr>
<td>adenovirus 40/41</td>
</tr>
<tr>
<td>rotavirus A</td>
</tr>
<tr>
<td>norovirus GI/GII</td>
</tr>
<tr>
<td><strong>Parasitic</strong></td>
</tr>
<tr>
<td><em>Cryptosporidium</em> spp.³</td>
</tr>
<tr>
<td><em>Entamoeba histolytica</em></td>
</tr>
<tr>
<td><em>Giardia lamblia</em>⁴</td>
</tr>
</tbody>
</table>

¹ *C. jejuni, C. coli* and *C. lari* only
² *S. boydii, S. sonnei, S. flexneri* and *S. dysenteriae*
³ *C. parvum* and *C. hominis* only
⁴ *G. lamblia* only (also known as *G. intestinalis* and *G. duodenalis*)
• Assay run time = 5 hours
• Hands on time = Between 45 minutes and 2.5 hours
• Turnaround time for results = variable
  – Batched testing, not performed on demand
  – TAT will depend on testing volumes and laboratory testing schedule

• Throughput = 96 samples + controls per run
• Open system
xTAG GPP Performance

Performance of the xTAG® Gastrointestinal Pathogen Panel, a Multiplex Molecular Assay for Simultaneous Detection of Bacterial, Viral, and Parasitic Causes of Infectious Gastroenteritis

Eric C. Claas¹, Carey-Ann D. Burnham², Tony Mazzulli¹, Kate Templeton⁴, and Francois Topin⁵*

• Multi-center study containing both adult and pediatric specimens
• 901 stool samples tested

Overall sensitivity was 94.3%
  – Not able to be determined for 3 of the targets
Overall specificity was 98.5%

BioFire FilmArray
Gastrointestinal (GI) Panel

(now acquired by bioMérieux)
FilmArray Gastrointestinal (GI) Panel

- Qualitative, PCR based assay
- Detects 22 bacterial, toxin, viral, and parasitic GI pathogens

- Approved specimens
  - stool samples in Cary Blair transport media

- FDA approved in 2014
FilmArray GI Panel
### FilmArray GI Panel Targets

#### Bacterial and Toxin
- *Campylobacter* spp.¹
- *Clostridium difficile* Toxin A/B
- *Plesiomonas shigelloides*
- *Salmonella* spp.
- *Yersinia enterocolitica*
- *Vibrio* spp.²
- Enteroaggregative *E. coli* (EAEC)
- Enteropathogenic *E. coli* (EPEC)
- Enterotoxigenic *E. coli* (ETEC) LT/ST
- Shiga-like toxin producing *E. coli* (STEC) stx1/stx2
- *Escherichia coli* 0157
- *Shigella* /Enteroinvasive *E. coli* (EIEC)

#### Parasitic
- *Cryptosporidium* spp.
- *Cyclospora cayetanensis*
- *Entamoeba histolytica*
- *Giardia lamblia*³

¹ *C. jejuni*, *C. coli* and *C. upsaliensis* only
² *V. cholerae*, *V. vulnificus*, and *V. parahaemolyticus* only
³ *G. lamblia* only (also known as *G. intestinalis* and *G. duodenalis*)

#### Viral
- Adenovirus 40/41
- Rotavirus A
- Norovirus GI/GII
- Sapovirus
- Astroivirus
FilmArray GI Panel

• Assay run time = 1 hour
• Hands on time = 2 minutes
• Turnaround time for results
  – Performed on demand

• Throughput = one sample per instrument
• Closed system
• Fully automated
• Scalable based on testing volumes
FilmArray GI Panel Performance

Multicenter Evaluation of the BioFire FilmArray Gastrointestinal Panel for Etiologic Diagnosis of Infectious Gastroenteritis

Sarah N. Buss, Amy Leber, Kimberle Chapin, Paul D. Fey, Matthew J. Bankowski, Matthew K. Jones, Margarita Rogatcheva, Kristen J. Kanack, Kevin M. Bourzac

- Multi-center study containing both adult and pediatric specimens
- 1556 stool samples tested

Overall sensitivity was $\geq 94.5\%$
  - Not able to be determined for 3 of the targets

Overall specificity was $\geq 97.1\%$

Looking to the future...

Evolution of FilmArray

FilmArray 1.0

FilmArray 2.0 (8 instruments)

FilmArray Torch (12-plex)

www.biofiredx.com
Nanosphere Verigene Enteric Pathogen (EP) Panel

(recently acquired by Luminex)
Verigene Enteric Pathogen (EP) Panel

• Qualitative, hybridization based assay
• Detects 9 bacterial, toxin, and viral GI pathogens

• Approved specimen
  – unformed stool specimens (liquid or soft) preserved in Cary Blair medium

• FDA approved in 2014
Verigene EP Panel
<table>
<thead>
<tr>
<th>Targets</th>
<th></th>
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<td></td>
</tr>
<tr>
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<td>²</td>
</tr>
<tr>
<td><em>Vibrio</em> spp.</td>
<td>³</td>
</tr>
<tr>
<td><em>Yersinia enterocolitica</em></td>
<td></td>
</tr>
<tr>
<td>Shiga Toxin 1 (stx1)</td>
<td></td>
</tr>
<tr>
<td>Shiga Toxin 2 (stx2)</td>
<td></td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
</tr>
<tr>
<td>rotavirus A</td>
<td></td>
</tr>
<tr>
<td>norovirus GI/GII</td>
<td></td>
</tr>
</tbody>
</table>

¹ *C. jejuni, C. coli* and *C. lari* only

² *S. boydii, S. sonnei, S. flexneri* and *S. dysenteriae*

³ *V. cholerae* and *V. parahaemolyticus* only
Verigene EP Panel

- Assay run time = <2 hours
- Hands on time = <5 minutes
- Turnaround time for results
  - Performed on demand
- Throughput = one sample per instrument
- Closed system
- Fully automated
- Scalable based on testing volumes
Verigene EP Panel

Verigene EP Performance vs. Reference Methods
(n=1,940)*

<table>
<thead>
<tr>
<th>TARGET</th>
<th>POSITIVE AGREEMENT (%)</th>
<th>NEGATIVE AGREEMENT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campylobacter Group</td>
<td>97.0</td>
<td>99.0</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td>97.3</td>
<td>99.5</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>98.4</td>
<td>99.0</td>
</tr>
<tr>
<td>Vibrio Group</td>
<td>91.5</td>
<td>99.9</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Toxins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiga Toxin 1 (stx1)</td>
<td>100</td>
<td>99.6</td>
</tr>
<tr>
<td>Shiga Toxin 2 (stx2)</td>
<td>97.3</td>
<td>99.8</td>
</tr>
<tr>
<td>Viruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norovirus (GI/GII)</td>
<td>94.8</td>
<td>99.7</td>
</tr>
<tr>
<td>Rotavirus (Group A)</td>
<td>96.3</td>
<td>99.9</td>
</tr>
</tbody>
</table>

- 1940 fresh, frozen, and spiked stool specimens from 7 geographically diverse sites were tested
- No peer reviewed publications available at this time
Looking to the future... Verigene EP Flex

<table>
<thead>
<tr>
<th>BACTERIA</th>
<th>VIRUSES</th>
<th>PARASITES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aeromonas spp.</td>
<td>Shigella spp.</td>
<td>Adenovirus F (40/41)</td>
</tr>
<tr>
<td>C. difficile (tcdA/tcdB)</td>
<td>Vibrio cholerae</td>
<td>Astrovirus</td>
</tr>
<tr>
<td>Campylobacter Group</td>
<td>Vibrio Group</td>
<td>Norovirus (GI/GII)</td>
</tr>
<tr>
<td>Enterotoxigenic E. coli (lt/st)</td>
<td>Yersinia enterocolitica</td>
<td>Rotavirus A</td>
</tr>
<tr>
<td>Plesiomonas shigelloides</td>
<td></td>
<td>Sapovirus (I, II, IV, V)</td>
</tr>
<tr>
<td>Salmonella spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiga Toxin 1 (stx1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiga Toxin 2 (stx2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- One Cartridge, Multiple Reporting Configurations
- You only pay for the group when you unveil the results
- Useful for testing different patient populations using the same assay

www.nanosphere.us
Summary of Platforms
### Summary of Platforms

**TABLE 2** Comparison of features between three commercial, FDA-cleared, multiplex platforms for the detection of gastrointestinal pathogens

<table>
<thead>
<tr>
<th>Feature</th>
<th>Verigene EP</th>
<th>FilmArray GI</th>
<th>xTAG GPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of FDA-cleared targets</td>
<td>9</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Processing (hands-on) time per run, min</td>
<td>&lt;5</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>Separate extraction required?</td>
<td>No</td>
<td>No</td>
<td>Yes (~45 min)</td>
</tr>
<tr>
<td>Time/run, h</td>
<td>~2</td>
<td>~1</td>
<td>~5</td>
</tr>
<tr>
<td>Throughput, specimens/run</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>96</td>
</tr>
<tr>
<td>Technology</td>
<td>PCR + gold nanoparticle hybridization</td>
<td>Nested PCR + melting curve</td>
<td>PCR + xTag (fluorescent bead-based detection)</td>
</tr>
<tr>
<td>Open or closed system</td>
<td>Closed</td>
<td>Closed</td>
<td>Open</td>
</tr>
<tr>
<td>Footprint</td>
<td>Small to moderate</td>
<td>Small</td>
<td>Moderate</td>
</tr>
<tr>
<td>List price per instrument, $</td>
<td>40,000&lt;sup&gt;c&lt;/sup&gt;</td>
<td>39,500</td>
<td>37,000</td>
</tr>
<tr>
<td>List price reagent cost per specimen, $</td>
<td>80&lt;sup&gt;d&lt;/sup&gt;</td>
<td>155&lt;sup&gt;d&lt;/sup&gt;</td>
<td>80–90&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> EP, enteric pathogen; GI, gastrointestinal; GPP, gastrointestinal pathogen panel.

<sup>b</sup> Scalable to increase throughput with additional instruments/processing modules. The FilmArray 2.0 system can connect up to 8 instruments to a single computer. The Verigene System allows for up to 32 Processor SP units to be connected to a single Verigene Reader.

<sup>c</sup> Includes the list price for both the Verigene Processor SP ($20,000) and the Verigene Reader ($20,000).

<sup>d</sup> Actual reagent price may be discounted based on the volume of samples tested.
Target Summary

<table>
<thead>
<tr>
<th>Target</th>
<th>Multiplex panel</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aeromonas</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Campylobacter</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Clostridium difficile</strong> (toxin A/B)</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Plesiomonas shigelloides</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Salmonella</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Yersinia enterocolitica</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>RUO</td>
</tr>
<tr>
<td><strong>Vibrio spp.</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>EAEC</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>EPEC</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>ETEC</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>STEC (stx₁ and stx₂)</strong></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>E. coli 0157</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>EIEC/Shigella</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Cryptosporidium</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Cyclospora cayetanensis</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Entamoeba histolytica</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Giardia lamblia</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Adenovirus 40/41</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Norovirus GI/GII</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Rotavirus A</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Sapovirus</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Astrovirus</strong></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
### Current Use

#### 2016 CAP GIP Survey

<table>
<thead>
<tr>
<th>Platform</th>
<th>Number of Participants</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>xTag GPP</td>
<td>29</td>
<td>12%</td>
</tr>
<tr>
<td>FilmArray GI Panel</td>
<td>181</td>
<td>74%</td>
</tr>
<tr>
<td>Verigene EP Panel</td>
<td>33</td>
<td>14%</td>
</tr>
</tbody>
</table>
BENEFITS, LIMITATIONS, AND CONSIDERATIONS
Increased Positivity Rates

• >50% of specimens tested by BioFire GI panel were positive for at least one target

• With xTAG GPP, positivity rates of GI pathogens increased by 2- to 4-fold compared to conventional methods

Increased Sensitivity

• xTAG GPP was found to be more sensitive than traditional testing for *Campylobacter, Salmonella, Clostridium difficile* toxin, norovirus and rotavirus

• Other molecular panels showed similar increases in sensitivity over traditional methods
Unexpected Results

• By casting a broad net, panel testing often alerts health care providers to unexpected causes of infectious gastritis
  – One study found that pathogen specific testing was not requested for 65% of positive targets found by xTAG GPP

Are these unexpected results clinically meaningful or just information?
Interpretation of New Targets

• Some panels include viruses that were not routinely tested in the past

• Clinical significance for some targets is an area of active research
  – EPEC, ETEC, EAEC, sapovirus
Detection of Co-infections

Study of the Biofire GI panel tested 1556 specimens
• 262 were positive for multiple targets
  – Highest co-infection rates with *C. difficile* and EPEC

<table>
<thead>
<tr>
<th>Number of positive targets</th>
<th>Number of specimens</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>724</td>
<td>46.5%</td>
</tr>
<tr>
<td>1</td>
<td>570</td>
<td>36.6%</td>
</tr>
<tr>
<td>2</td>
<td>199</td>
<td>12.8%</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>0.6%</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>0.2%</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

When many targets are detected, what is clinically significant?

Bacterial and Viral Shedding in the Stool

• Molecular tests detect live and dead pathogens

• Asymptomatic shedding of bacterial and viral pathogens can last weeks to months after the patient has resolved symptoms

• Shedding is even more prolonged immunocompromised patients

How do you determine active infection?
Antimicrobial Susceptibility Testing

• AST cannot be obtained from bacteria identified by molecular panels

• Due to increased sensitivity of the assay, bacterial pathogens will not necessarily be recovered from bacterial stool culture
**Clostridium difficile**

....to report or not to report

xTAG GPP and FilmArray GI panel contain targets for *C. difficile*

- Both test for *C. difficile* toxin A and B genes

- Because GI panel testing can be ordered for many reasons, there are not age restrictions
  - Particularly for children < 1 year of age

- Stool consistency cannot be assessed if stool is submitted in Cary Blair medium
**Clostridium difficile**

....to report or not to report

A. Should labs view *C. difficile* results, but not report
   – Physicians would need to order a stand alone *C. difficile* PCR at additional cost to the patient

B. Should labs report *C. difficile* results provided by the panel
   – But with the knowledge that some testing is inappropriate
   – could result in unnecessary treatment
Reportable Pathogens

• Certain bacterial isolates are required to be sent to the state health department if identified
  – Shiga toxin-producing *E. coli*
  – *Vibrio* spp.

• Who is responsible for isolating the organism?
  – Clinical laboratory
  – Public health laboratory

What if the pathogen is detected by a GI panel but cannot be isolated in culture?
Outbreak Detection

- Outbreaks may be recognized earlier due to sensitivity of assay and shortened time to results
- No bacterial isolate available for PFGE or sequence typing
Patient Benefits

- Possible cost savings
  - Depends on how many laboratory tests the physician would have ordered without the panel

- Viral or parasitic positive result
  - Could result in prevention or discontinuation of antibiotic therapy

- Rapid bacterial positive result
  - Could result in earlier initiation of antibiotic therapy

- Any rapid result could prevent spread to others
  - Nosocomial spread or outpatient patient contacts
Institutional Benefit

- Reported $100,000 cost savings per year
- Increased cost of testing for GI pathogens offset by removing patients from isolation

A cost benefit analysis of the Luminex xTAG Gastrointestinal Pathogen Panel for detection of infectious gastroenteritis in hospitalised patients

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J. of Infection. 2014. doi:10.1016/j.jinf.2014.11.009
Summary

• Implementation of molecular panels allows for rapid detection of GI pathogens
  – Casts a broad net and removes pre-analytic step of physician test selection
  – Decreases hands on time for the laboratory

• Panels have increased sensitivity of pathogen detection

• Interpretation of results can be complicated
  – Active infection vs. colonization vs. asymptomatic shedding
  – Multiple positive targets
  – Clinical significance of some targets is an area of active research
Thank you—

- Morgan Pence and the SWACM organizing committee

- Shari Young, Sandy Hipo, Kelly Plough, and the microbiology technologists at Children’s Medical Center Dallas

- Rita Hollaway, Dominick CAVUOTI, Paul Southern and my clinical pathology colleagues at UT Southwestern Medical Center