Hypothetical Impact of a Molecular Diagnostic for Pediatric Acute Gastroenteritis: The FilmArray GI Panel Hy-IMPACT Study

MI Ardura[1,2], K Everhart[3], K Bourzac[4], A Leber[1,3]

Departments of [1]Pediatrics and [2]Infectious Diseases, [3]Pathology, Nationwide Children's Hospital and The Ohio State University and [4]BioFire Diagnostics, LLC, Salt Lake City, UT

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abstract

Background: Diarrheal disease is common in pediatrics, but an infectious etiology is not always confirmed. The FilmArray® Gastrointestinal Panel (FA) is a rapid, highly multiplexed test for bacteria (8 results; including *C. difficile),* diarrheagenic *E. coli* (dEC) (6 results), parasites (4 results), and viruses (5 results).
Methods: We performed a retrospective analysis of stool samples tested by FA and compared with conventional testing (CT) ordered as standard of care. Medical record review was performed in a subset of patients with positive results to model what impact having the FA results at initial presentation might have had on patient management.
Results: An organism was detected in 63% of 793 stool samples; 23% had multiple organisms detected. For bacterial targets for which culture or antigen testing was done, FA detected 47 analytes missed by culture and 12 analytes for E coli O157/ STEC antigen. For viral and parasitic targets with CT available (Adeno-, Rota- and Norovirus, *Giardia*, *Cryptosporidium* and *E. histolytica*), an additional 100 targets were detected by FA that were not ordered by the physician; 13 targets detect by FA were missed by CT. Among novel analytes for which CT is not available (Astro-, Sapovirus, and dEC), 43 (5%) viral and 296 (37%) dEC targets (most commonly EPEC) were detected.
Clinical data was available for review in 172 patients with at least one positive target, 68 (40%) had ≥ 2 analytes detected by FA. The median age was 3 y [range 0.2-24], 34 (20%) had an underlying medical condition and presented with a history of fever (n=29, 17%) or blood in stools (n= 43, 25%). FA detected an analyte in 72 (42%) patients who did not have a diagnosis found by CT. In 93 (54%) patients, dEC was detected and was the sole pathogen in 39 (23%) patients. By CT, 53 (31%) patients had a positive result, 29 received an antibiotic a median of 1 day (range 0-8) after CT results were reported. Based on results of FA detection, an antibiotic may have been prescribed at the initial encounter to 66 patients. 21 patients (12%) had repeated encounters related to GI illness.
Conclusions: Application of FA in pediatric patients with GI illness may allow for an improved diagnostic yield, timely and target antimicrobial therapy, and patient education. Further data is needed regarding the implication of dEC detection.

background

- Diarrheal illnesses are common in the pediatric population, but an infectious etiology is not always ascertained.
- The FilmArray Gastrointestinal Panel (FA) is a rapid (TAT ~ 1 hr), highly multiplexed test that allows detection of:

Bacteria	**Diarrheagenic *E. coli/Shigella***
Campylobacter (*C. jejuni, C. coli,* and *C. upsaliensis*)	Shiga toxin-producing *E. coli* (STEC) *stx1/stx2*
Clostridium difficile (toxigenic)	*E. coli* O157
Plesiomonas shigelloides	Enterotoxigenic *E. coli* (ETEC) *lt/st*
Salmonella	Enteropathogenic *E. coli* (EPEC)
Vibrio	Enteroaggregative *E. coli* (EAEC)
V. cholerae	*Shigella*/Enteroinvasive *E. coli* (EIEC)
Yersinia enterocolitica	**Viruses**
Parasites	Adenovirus F40/41
Cryptosporidium	Astrovirus
Cyclospora cayetanensis	Norovirus GI/GII
Entamoeba histolytica	Rotavirus A
Giardia lamblia	Sapovirus

methods

- Retrospective analysis of stool samples submitted as standard of care for routine stool culture at Nationwide Children's Hospital from May to Sept.2013.
- Stool samples in Cary Blair media were tested by FilmArray [(FA) as part of the clinical trial to support product registration (FDA 510k)] and compared with conventional testing (CT).
- Medical record review was performed by an infectious disease clinician in a subset of patients who were followed at Nationwide Children's Hospital and had both clinical data available and positive FA results in order to model what impact having the FA results at initial presentation might have had on patient management. *Of note*: Aeromonas was included in the RUO reagents and in this analysis but is not a reported analyte in the final IVD product.

results

Study Population

- 793 patients were enrolled in clinical trial for FDA clearance of the GI panel.
- Of 499 positive samples, 172 (22%) had clinical data available for additional chart review.

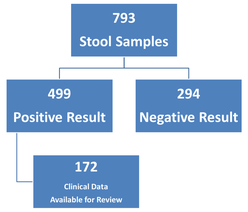


Table 1. Results of Conventional Testing (CT) versus Film Array (FA), n=793

Pathogen	# ordered CT	# pos CT	# pos FA	# pos missed by FA	# pos missed by CT	# pos not ordered at all
Bacteria						
*Aeromonas**	793	14	30	0	16	0
Campylobacter	793	14	25	0	11	0
C. difficile toxin A/B	278	54	147	0	12	81
Plesiomonas shigelloides	793	1	9	0	8	0
Salmonella	793	12	16	0	4	0
Vibrio	0	0	0	0	0	0
Vibrio cholerae	0	0	0	0	0	0
Yersinia enterocoliticia	793	2	1	1	0	0
Diarrheagenic *E. coli/Shigella*						
EAEC	na	na	61	na	na	na
EPEC	na	na	224	na	na	na
ETEC	na	na	11	na	na	na
STEC	793	15	27	0	12	0
E. coli O157	793	2	3	0	1	0
Shigella/EIEC	793	20	29	0	9	0
Parasites						
Cryptosporidium	381	8	16	1	3	5
Cyclospora cayetanensis	0	na	0	0	0	0
Entamoeba histolytica	381	0	0	0	0	0
Giardia lamblia	381	6	11	0	4	1
Viruses						
Adenovirus F 40/41	8	1	44	0	1	43
Astro virus	0	na	5	0	na	na
Noroviurs GI/GII	5	0	46	0	0	41
Rotavirus	53	2	12	1	0	12
Sapovirus	0	na	38	0	na	na

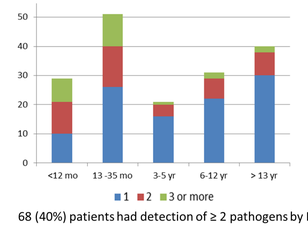
*not FDA cleared; na = not applicable

Table 2. Clinical data for 172 evaluable patients

Clinical Data	N=172
Age (in years; median [range])	3 [0.1-24]
Male : Female (M:F)	97 M :75 F
Known underlying medical condition*	34 (20%)
Clinical Presentation	**(N, %)**
Diarrhea	98 (57%)
Vomiting	41 (24%)
Change in stool pattern(intermittent loose)*	38 (22%)
Blood in stool (by hx or guaiac)	64 (37%)
Abdominal pain only	20 (12%)
Acute symptoms (≤ 7 days) : chronic (≥ 30 days)	67 (39%) : 59 (34%)
History of fever; Fever at presentation	29 (17%) ; 11 (6%)
Contributing epidemiological history	60 (35%)
Daycare	26 (15%)
Recent international travel	14 (8%)
Antibiotics in the previous 2 weeks	8 (5%)
Exposure to known pathogen#	5 (3%)

* Most commonly, Inflammatory Bowel Disease (IBD, n=27), other immunocompromised host (n=7);
#*Shigella* spp. in daycare

Figure 1. FA detection by age



68 (40%) patients had detection of ≥ 2 pathogens by FA

Table 3. FA detections missed by CT

Viral	# samples	Bacterial	# samples	Other	# samples
Adeno	15	Aeromonas	5	Crypto	4
Astro	2	Campy	5	Giardia	3
Norovirus	21	C diff*	6		
Rota	2	Shigella	3		
Sapo	13	STEC	1		
		Plesio	2		
Totals:	**53 viral**		**22 bacterial**		**7 parasitic**

* Per AAP testing recommendations; EPEC, ETEC, and EAEC not included

Figure 2. Clinical correlates to analytes detected by FA, n=172

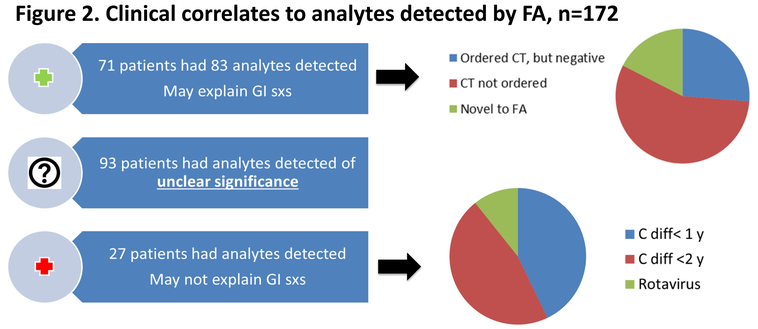
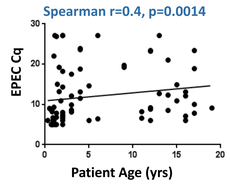


Figure 3. Unclear clinical significance of EPEC/EAEC detection



EPEC and EAEC Median Cq			p-value
acute vs chronic symptoms	8.2	10.9	0.2
sole vs co-detection	10.9	8.8	0.3
bloody stools vs non-bloody	12.7	8.8	0.39
IBD pts vs all others	10.9	9	0.58

* Cq is based on comparator PCR assay

Table 3. Modeling FA results to hypothetical changes in management

Variable	Conventional	FA	
Time from stool collection to final diagnosis (day)	3 [0-14]	0	P < 0.001
Antibiotics indicated and given when final results known	40 pts	66 pts	**26 (15%) additional pts warranted abx tx**
Time from stool specimen to antibiotic (days)	1 [0-8]	0	P < 0.001
Additional etiology found	-	**72 pts**	
Unnecessary* antibiotics given	7 pts	27 pts	**7 (4%) of patients received wrong abx or not needed**

* Unnecessary antibiotics = incorrect antibiotic given for analyte detected or an antibiotic was not indicated (viral detection only)

conclusions

- In **793** stool samples tested, **FA detected an additional 481 analytes** missed by conventional testing methods because of lower sensitivity or the testing was not available or not ordered.
- Among the subset of **172** patients with varied abdominal complaints, **an additional 72 (42%) patients** had a possible etiology identified by FA, that was not detected by CT.
  - Results of FA would have changed management in 33 (19%) patients at the initial encounter; timely antibiotics would have been prescribed at initial encounter for 66 patients.
  - Co-detection of analytes was common. The most common co-detection was *C. difficile* + EPEC, occurring most frequently in children ≤ 5 years of age. Co-detection of viruses makes it difficult to determine if viruses detected are causing disease/symptoms or represent asymptomatic shedding.
  - In our cohort, detection of EPEC or EAEC lacked specificity to determine causality of the varied chief complaints. There was a statistical correlation between Cq values and patient age. However, no significant differences were found between EPEC/EAEC Cq values and acute vs chronic symptoms, underlying GI disease, nor detection as a sole or co-pathogen.
  - The significance of *C. difficile* detection in infants and children ≤ 2 yrs and EPEC/EAEC in stool samples in non-endemic settings requires further clinical correlation and prospective study.
  - Application of FA for test of cure in outbreaks of *Shigella* (off-label use) showed detection 10-14 days after negative cultures. FA may detect rotavirus in recently vaccinated infants.
  - FA performance characteristics in our population may be influenced by clinical presentation: only 39% of patients had acute diarrheal symptoms at time of testing.