Gastrointestinal Pathogen (GIP) Panel Multiplex Nucleic Acid Based Assay
First Coast Service Options, Inc.

On April 27, 2019, the JN Contractor Advisory Committee (CAC) will convene to consider the quality of evidence and strength of recommendation of the published literature for the use of GIP multiplex panels for diagnostic testing in Medicare patients with diarrhea. Diarrhea is a common complaint and is a frequent reason to seek medical care. Pathogens, including bacteria, parasites, and viruses can cause infectious diarrhea. Most episodes of diarrhea will resolve without medical treatment. In the past, diagnostic testing for these pathogens was accomplished by techniques such as stool culture or examination for ova and parasites. Multiplex nucleic acid based assays are now available to detect a number of these pathogens in a single sample, with results available in much shorter time frames. Diagnostic tests are medically reasonable and necessary when they affect patient management to improve health outcomes. Health outcomes of interest include reduction of severity of disease, symptom duration, and disease transmission.

See Appendix A below for definitions and currently available panels.

Voting Questions:

For each voting question, please use the following scale identifying your level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence.

1	—	*2*	—	*3*	—	*4*	—	*5*
Low Confidence				*Intermediate*				*High Confidence*

We ask for the CAC members to submit their responses to the voting questions following the CAC meeting no later than Friday, May 10, 2019 by email to Medical.Policy@fcso.com.

1. How confident are you that there is adequate published evidence that a GIP panel (**3 to 5 targets**) improves health outcomes during the
    a. **initial** evaluation of **immune competent** Medicare patients
    b. **subsequent** evaluation of **immune competent** Medicare patients with:
        i. Acute diarrhea?
        ii. Persistent diarrhea?
        iii. Chronic diarrhea?

2. If less than intermediate confidence (< 3) is noted in question #1, how confident are you that each of the following concerns regarding the GIP panel (3 to 5 targets) has inadequate evidence?
    a. Clinically important finding
    b. Diagnostic specificity
    c. Diagnostic sensitivity
    d. False negative rate
    e. False positive rate

3. If less than intermediate confidence (< 3) is noted in question #1, how confident are you that each of the following additional GIP panel (3 to 5 targets) evidence is needed?
    a. Systematic Reviews and Meta-analyses
    b. Randomized Control Trials (RCT)
    c. Observational Studies

4. If at least intermediate confidence (≥ 3) is noted in question #1, please discuss clinical parameters that would impact the choice of the GIP panel (3 to 5 targets).

5. How confident are you that there is adequate published evidence that a GIP panel (**3 to 5 targets**) improves health outcomes during the
    a. **initial** evaluation of **immunosuppressed** Medicare patients
    b. **subsequent** evaluation of **immunosuppressed** Medicare patients with:
        i. Acute diarrhea?
        ii. Persistent diarrhea?
        iii. Chronic diarrhea?

6. If less than intermediate confidence (< 3) is noted in question #5, how confident are you that each of the following concerns regarding the GIP panel (3 to 5 targets) has inadequate evidence?
    a. Clinically important finding
    b. Diagnostic specificity
    c. Diagnostic sensitivity
    d. False negative rate
    e. False positive rate

7. If less than intermediate confidence (< 3) is noted in question #5, how confident are you that each of the following additional GIP panel (3 to 5 targets) evidence is needed?
    a. Systematic Reviews and Meta-analyses
    b. Randomized Control Trials (RCT)
    c. Observational Studies

8. If at least intermediate confidence (≥ 3) is noted in question #5, please discuss clinical parameters that would impact the choice of the GIP panel (3 to 5 targets).

9. How confident are you that there is adequate published evidence that a GIP panel (**6 to 11 targets**) improves health outcomes during the
    a. **initial** evaluation of **immune competent** Medicare patients
    b. **subsequent** evaluation of **immune competent** Medicare patients with:
        i. Acute diarrhea?
        ii. Persistent diarrhea?
        iii. Chronic diarrhea?

10. If less than intermediate confidence (< 3) is noted in question #9, how confident are you that each of the following concerns regarding the GIP panel (6 to 11 targets) has inadequate evidence?
    a. Clinically important finding
    b. Diagnostic specificity
    c. Diagnostic sensitivity
    d. False negative rate
    e. False positive rate

11. If less than intermediate confidence (< 3) is noted in question #9, how confident are you that each of the following additional GIP panel (6 to 11 targets) evidence is needed?
    a. Systematic Reviews and Meta-analyses
    b. Randomized Control Trials (RCT)
    c. Observational Studies

12. If at least intermediate confidence (≥ 3) is noted in question #9, please discuss clinical parameters that would impact the choice of the GIP panel (6 to 11 targets).

13. How confident are you that there is adequate published evidence that a GIP panel (**6 to 11 targets**) improves health outcomes during the
    a. **initial** evaluation of **immunosuppressed** Medicare patients
    b. **subsequent** evaluation of **immunosuppressed** Medicare patients with:
        i. Acute diarrhea?
        ii. Persistent diarrhea?
        iii. Chronic diarrhea?

14. If less than intermediate confidence (< 3) is noted in question #13, how confident are you that each of the following concerns regarding the GIP panel (6 to 11 targets) has inadequate evidence?
    a. Clinically important finding
    b. Diagnostic specificity
    c. Diagnostic sensitivity
    d. False negative rate
    e. False positive rate

15. If less than intermediate confidence (< 3) is noted in question #13, how confident are you that each of the following additional GIP panel (6 to 11 targets) evidence is needed?
    a. Systematic Reviews and Meta-analyses
    b. Randomized Control Trials (RCT)
    c. Observational Studies

16. If at least intermediate confidence (≥ 3) is noted in question #13, please discuss clinical parameters that would impact the choice of the GIP panel (6 to 11 targets).

17. How confident are you that there is adequate published evidence that a GIP panel (**12 to 25 targets**) improves health outcomes during the
    a. **initial** evaluation of **immune competent** Medicare patients
    b. **subsequent** evaluation of **immune competent** Medicare patients with:
        i. Acute diarrhea?
        ii. Persistent diarrhea?
        iii. Chronic diarrhea?

18. If less than intermediate confidence (< 3) is noted in question #17, how confident are you that each of the following concerns regarding the GIP panel (12 to 25 targets) has inadequate evidence?
    a. Clinically important finding
    b. Diagnostic specificity
    c. Diagnostic sensitivity
    d. False negative rate
    e. False positive rate

19. If less than intermediate confidence (< 3) is noted in question #17, how confident are you that each of the following additional GIP panel (12 to 25 targets) evidence is needed?
    a. Systematic Reviews and Meta-analyses
    b. Randomized Control Trials (RCT)
    c. Observational Studies

20. If at least intermediate confidence (≥ 3) is noted in question #17, please discuss clinical parameters that would impact the choice of the GIP panel (12 to 25 targets).

21. How confident are you that there is adequate published evidence that a GIP panel (**12 to 25 targets**) improves health outcomes during the
    a. **initial** evaluation of **immunosuppressed** Medicare patients
    b. **subsequent** evaluation of **immunosuppressed** Medicare patients with:
        i. Acute diarrhea?
        ii. Persistent diarrhea?
        iii. Chronic diarrhea?

22. If less than intermediate confidence (< 3) is noted in question #21, how confident are you that each of the following concerns regarding the GIP panel (12 to 25 targets) has inadequate evidence?
    a. Clinically important finding
    b. Diagnostic specificity
    c. Diagnostic sensitivity
    d. False negative rate
    e. False positive rate

23. If less than intermediate confidence (< 3) is noted in question #21, how confident are you that each of the following additional GIP panel (12 to 25 targets) evidence is needed?
    a. Systematic Reviews and Meta-analyses
    b. Randomized Control Trials (RCT)
    c. Observational Studies

24. If at least intermediate confidence (≥ 3) is noted in question #21, please discuss clinical parameters that would impact the choice of the GIP panel (12 to 25 targets).

25. How confident are you that there is adequate published evidence that repeating a GIP panel improves health outcomes in immune competent Medicare patients?

26. How confident are you that there is adequate published evidence that repeating a GIP panel improves health outcomes in immunosuppressed Medicare patients?

Appendix A

Definitions from the American College of Gastroenterology (ACG) 2019:

Acute diarrhea lasts less than 2 weeks.

Persistent diarrhea lasts between 2 and 4 weeks.

Chronic diarrhea lasts longer than 4 weeks.

Current Procedural Terminology (CPT) code descriptors:

87505 Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets

87506 Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets

87507 Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (eg, Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets

Statistics in Medicine Definitions:

Clinically important finding - has implications for patient care

Diagnostic specificity - the probability that a diagnostic test result will be negative when the disease is not present

Diagnostic sensitivity - the probability that a diagnostic test result will be positive when the disease is present

False negative rate - the probability that a diagnostic test result will be negative when the disease is present

False positive rate - the probability that a diagnostic test result will be positive when the disease is not present

Available Panels:

BD Max Enteric Bacterial Panel

• *Salmonella* spp. - (*SpaO* gene target)
• *Campylobacter* spp.- *(C. jejuni, C. coli*) - *(Campylobacter* specific *tuf* gene target)
• *Shigella* spp./*Enteroinvasive Escherichia coli* (EIEC) - (*ipaH* gene target)
• Shiga toxin 1 (*stx*1) / Shiga toxin 2 (*stx*2) genes (found in Shiga toxin-producing E. coli [STEC]) as well as *Shigella dysenteriae*, which can possess a Shiga toxin gene (*stx*) that is identical to the *stx*1 gene of STEC.

BD Max Extended Enteric Bacterial Panel

• *Plesiomonas shigelloides*
• *Vibrio (V. vulnificus, V. parahaemolyticus, and V. cholerae)*
• *Enterotoxigenic Escherichia coli (ETEC) heat-labile enterotoxin (LT)/ heat-stable enterotoxin (ST) genes*
• ·*Yersinia enterocolitica*

BD Max Enteric Viral Panel

• Norovirus GI & GII
• Rotavirus A
• Adenovirus F40/41
• Sapovirus (genogroups I, II, IV, V)
• Human Astrovirus (hAstro)

FilmArray Gastrointestinal Panel (GI)

• *Campylobacter* (*C. jejuni/C. coli/C. upsaliensis*)
• *Clostridium difficile* (*C. difficile*) toxin A/B
• *Plesiomonas shigelloides*
• *Salmonella*
• *Vibrio* (*V. parahaemolyticus/V. vulnificus/V. cholerae*) including specific identification of *Vibrio cholerae*
• *Yersinia enterocolitica*
• Enteroaggregative *Escherichia coli* (EAEC)
• Enteropathogenic *Escherichia coli* (EPEC)
• Enterotoxigenic *Escherichia coli* (ETEC) *lt/st*
• Shiga-like toxin-producing *Escherichia coli* (STEC) *stx1/stx2* (including specific identification of the *E. coli* O157 serogroup within STEC)
• *Shigella/*Enteroinvasive *Escherichia coli* (EIEC)
• *Cryptosporidium*
• *Cyclospora cayetanensis*
• *Entamoeba histolytica*
• *Giardia lamblia* (also known as *G. intestinalis* and *G. duodenalis*)
• Adenovirus F 40/41
• Astrovirus
• Norovirus GI/GII
• Rotavirus A
• Sapovirus (Genogroups I, II, IV, and V)

Great Basin Stool Bacterial Pathogens Panel

• *Campylobacter* (*C. coli*/ *C. jejuni*)
• *Salmonella*
• Shiga toxin 1 (stx1)
• Shiga toxin 2 (stx2)
• *Escherichia coli* serotype O157 (when stx1 or stx2 are detected)
• *Shigella*

Progastro SSCS Assay

• *Salmonella*
• *Shigella*
• *Campylobacter* (*C. jejuni and C. coli* only, undifferentiated)
• Shiga toxin 1 (stx1)
• Shiga toxin 2 (stx2)

Verigene Enteric Pathogen Nucleic Acid Test (EP)

• *Campylobacter* Group (comprised of *C. coli*, *C. jejuni*, and *C. lari*)
• *Salmonella* species
• *Shigella* species (including *S. dysenteriae*, *S. boydii*, *S. sonnei*, and *S. flexneri*)
• *Vibrio* Group (comprised of *V. cholerae* and *V. parahaemolyticus*)
• *Yersinia enterocolitica*
• Shiga toxin 1 gene and Shiga toxin 2 gene virulence markers
• Norovirus GI/GII
• Rotavirus A

XTAG Gastrointestinal Pathogen Panel (GPP)

• *Campylobacter* (*C. jejuni*, *C. coli* and *C. lari* only)
• *Clostridium difficile* (*C. difficile*) toxin A/B
• *Cryptosporidium* (*C. parvum* and *C. hominis* only)
• *Escherichia coli* (*E. coli*) O157
• Enterotoxigenic *E. coli* (ETEC) LT/ST
• *Giardia* (*G. lamblia* only – also known as *G. intestinalis* and *G. duodenalis)*
• Norovirus GI/GII
• Rotavirus A
• *Salmonella*
• Shiga-like Toxin producing *E. coli* (STEC) stx 1/stx 2
• *Shigella* (*S. boydii*, *S. sonnei*, *S. flexneri* and *S. dysenteriae*)
• *Vibrio cholerae* (*V. cholerae*) cholera toxin gene (ctx)
• Adenovirus 40/41
• *Entamoeba histolytica* (*E. histolytica*)