August 11, 2019

Debra Patterson, MD
Medical Director
Novitas Solutions Medical Policy Department
Suite 400
707 Grant Street
Pittsburg, PA 15219
ProposedLCDComments@novitas-solutions.com

Re: Proposed Local Coverage Determination (LCD): Gastrointestinal Pathogen (GIP) Panels Utilizing Multiplex Nucleic Acid Amplification Techniques (NAATs) (DL38229)

Dear Dr. Patterson:

Thank you for the opportunity to review and comment on Novitas Solutions' proposed coverage policy for Gastrointestinal Pathogen (GIP) Panels Utilizing Multiplex Nucleic Acid Amplification Techniques (NAATs) (DL38229). The American Gastroenterological Association (AGA), American Society for Microbiology (ASM), Association for Molecular Pathology (AMP), Association of Public Health Laboratories, (APHL); College of American Pathologists (CAP), Infectious Diseases Society of America (IDSA), and Pan American Society for Clinical Virology (PASCV), representing multiple areas of practice, have collaborated to present the most thorough analysis for your draft local coverage determination (LCD). The members of the six organizations developing these comments are subject matter experts in diagnosis and treatment of the gastrointestinal conditions covered by this policy and its possible implementation will directly impact their patients and practices. We are submitting joint comments because our organizations share the same concerns regarding this draft LCD. We appreciate the effort that has gone into the development of this policy, and we offer the following recommendations for Novitas Solutions' consideration.

We understand that this LCD was developed with input from Carrier Advisory Committee members and subject matter experts, as part of a new development LCD process outlined in the recent changes to Chapter 13 of the Program Integrity Manual. Upon our review, this dLCD is a positive product to that process. We applaud Novitas Solutions' efforts to clarify coverage for GIP panels utilizing multiplex NAATs. Coverage of GIP testing of twelve or more targets is particularly important for patients with an immunocompromised medical condition. However, with regard to coverage of up to eleven targets for the evaluation of Medicare beneficiaries, the undersigned organizations have some questions and recommendations on some of the coverage indications, limitations, and summary of the evidence outlined in the draft policy; from our review, some sections do not appropriately align with current clinical practice.

Coverage Limitations

The policy lists five limitations that are considered not medically reasonable and necessary. Below we provide either recommendations with supporting evidence and/or seek clarification for some of the coverage limitations within the draft policy.

- **Coverage limitation #2:** Gastrointestinal pathogen (GIP) panels utilizing multiplex NAATs are not medically reasonable and necessary for persistent or chronic diarrhea.

  Comments and Recommendations:
  We recommend Novitas allow for coverage of panels utilizing multiplex NAATs for persistent or chronic diarrhea when medically reasonable and necessary.

  The Background Section of the dLCD defines both persistent and chronic diarrhea. Persistent diarrhea is defined as lasting between fourteen (14) and thirty (30) days and chronic diarrhea is defined as lasting longer than thirty days (Riddle et al, 2016). Patients with more persistent or chronic diarrhea can have microorganisms that necessitate detection by GIP panels utilizing NAATs with eleven or fewer targets. In clinical practice, providers consider using those tests for patients that have had these symptoms for longer than two weeks, especially in travelers with persistent symptoms. Additionally, when persistent diarrhea is present, culture-independent testing, including NAATs, is recommended (Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea, 2017).

- **Coverage Limitation #3:** Gastrointestinal pathogen (GIP) panels utilizing multiplex NAATs are not medically reasonable and necessary for asymptomatic Medicare beneficiaries or for Medicare beneficiaries who have symptoms other than diarrhea.

  Comments:
  Gastroenteritis can present as symptoms other than diarrhea than those listed in the Covered Indications section of the draft LCD, including weakness, nausea, constipation, weight loss, and vomiting. Therefore, these symptoms should not exclude NAATs from being covered by Medicare (Table 3, Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea, 2017). For example, clinical presentation of

abdominal pain can be indicative of pathogens such as STEC, *Salmonella, Shigella, Campylobacter, Yersinia,* noncholera *Vibrio* species, *Clostridium difficile* and nausea . **We recommend that Novitas work to align the coverage indications and limitations with Table 3 of the IDSA guidelines to ensure the symptoms listed in the coverage policy are consistent with GIPs.**

- **Coverage Limitation #5:** Performance of more than one gastrointestinal pathogen (GIP) panel utilizing multiplex NAATs on the same date of service is not medically reasonable and necessary.

  Comments and Recommendations:
  We seek clarification as to how this limitation would be implemented and whether it would affect commercially available assays and laboratory developed testing procedures that are designed or available in modules, each having 3-5 targets. In certain clinical circumstances, it is medically reasonable to use assays in a stepwise fashion (i.e., reflex to next module if negative) on the same day of service. For example, in part based on prior guidance, the BD Max system has divided its enteric assays into five separate panels covering 1) enteric bacteria, 2) extended enteric bacteria, 3) enteric parasites, 4) enteric viruses, and 5) *C. difficile* (https://moleculardiagnostics.bd.com/syndromic-solutions/enteric-solutions/). Therefore, from our view, this limitation conflicts with current clinical practice and test design. **We encourage Novitas to ensure in its final LCD and related coding articles that stepwise testing utilizing smaller panels on the same date of service be allowed.**

Summary of Evidence

The policy provides a robust evidence summary. However, our organizations provide language recommendations on a few areas within this section.

- The policy provides evidence to support the following statement, "NAATs for the detection of *C. difficile* have reported sensitivity of 93%-100%."

  In response to additional supporting evidence, we recommend Novitas modify the above sentence to read as follows: (Please note: underlined text indicates the recommended additional language)

  NAATs for the detection of *C. difficile* determine whether a *C. difficile* strain carries the toxin B gene. NAATs have reported sensitivity of 93%-100%, but specificity is low because the tests do not determine whether the toxin is being actively produced in vivo and toxigenic strains of *C. difficile* can colonize patients without causing disease (Shim et al., 1998, Kyne et al., 2000, Leekha et al., 2013).

- The policy also provides supporting evidence regarding coverage of GIP testing for immunocompromised patient with diarrhea. The policy states, "For immunocompromised people with diarrhea, a broad differential diagnosis is recommended for evaluation of stool specimens by culture, viral studies and examination for parasites. People with acquired immune

deficiency syndrome (AIDS) with persistent diarrhea should undergo testing for additional organisms including, but not limited to, *Cryptosporidium, Cyclospora, Cystoisospora, microsporidia, Mycobacterium avium complex*, cytomegalovirus (CMV)."

In response to additional supporting evidence, we recommend Novitas modify the above sentence to read as follows: (Please note: underlined text indicates the recommended additional language)

For immunocompromised people with diarrhea, a broad differential diagnosis is recommended for evaluation of stool specimens by culture, viral studies and examination for parasites. People with acquired immune deficiency syndrome (AIDS) or otherwise immunocompromised, with persistent diarrhea should undergo testing for additional organisms including, but not limited to, *Cryptosporidium, Cyclospora, Cystoisospora, microsporidia, Mycobacterium avium complex*, cytomegalovirus (CMV), norovirus, astrovirus, sapovirus and adenovirus (Daniel-Wayman et al, 2018).

ICD-10 Coding

We request that additional ICD-10 codes be added to the local coverage article A56642 including, but not limited to the following list:

A00.0 Cholera due to Vibrio cholerae 01, biovar cholera
A01.00 Typhoid fever, unspecified
A01.1 Typhoid meningitis
A01.2 Typhoid fever with heart involvement
A01.3 Typhoid pneumonia
A01.4 Typhoid arthritis
A02.0 Salmonella enteritis
A02z1 Salmonella sepsis
A02.20 Localized salmonella infection, unspecified
A02.22 Salmonella pneumonia
A02.8 Other specified salmonella infections
A02.9 Salmonella infection, unspecified
A03.0 Shigellosis due to Shigella dysenteriae
A03.1 Shigellosis due to Shigella flexneri
A03.2 Shigellosis due to Shigella boydii
A03.3 Shigellosis due to Shigella sonnei
A03.8 Other shigellosis
A03.9 Shigellosis, unspecified
A04.0 Escherichia coli enteropathogenic
A04.1 Escherichia coli enterotoxigenic
A04.2 Escherichia coli enteroinvasive
A04.3 Escherichia coli enterohemorrhagic
A04.4 Escherichia coli enteroaggregative

A04.5 Escherichia coli
A04.6 Yersinia enterocolitica
A04.7 Clostridium difficile
A04.9 Bacterial intestinal infection, unspecified
A05.0 Foodborne staphylococcal intoxication
A05.1 Botulism food poisoning
A05.2 Foodborne Clostridium perfringens [Clostridium welchii] intoxication
A05.3 Foodborne Vibrio parahaemolyticus intoxication
A05.4 Foodborne Bacillus cereus intoxication
A05.5 Foodborne Vibrio vulnificus intoxication
A05.8 Other specified bacterial foodborne intoxications
A05.9 Bacterial foodborne intoxication, unspecified
A06.0 Acute amebic dysentery
A07.1 Giardiasis [lambliasis]
A07.2 Cryptosporidiosis
A07.8 Other specified protozoal intestinal diseases
A08.0 Rotaviral enteritis
A08.2 Adenoviral enteritis
A08.11 Acute gastroenteropathy due to Norwalk agent
A08.19 Acute gastroenteropathy due to other small round viruses
A08.31 Calicivirus enteritis
A08.32 Astrovirus enteritis
A08.39 Other viral enteritis
A08.8 Other specified intestinal infections
A09 Infectious gastroenteritis and colitis, unspecified
A28.2 Extraintestinal yersiniosis
A49.1 Methicillin susceptible Staphylococcus aureus infection, unspecified site
A49.2 Methicillin resistant Staphylococcus aureus infection, unspecified site
A49.3 Mycoplasma infection, unspecified site
A49.9 Bacterial infection, unspecified
A87.0 Enteroviral meningitis
A87.8 Other viral meningitis
A87.9 Viral meningitis, unspecified
A88.8 Other specified viral infections of central nervous system

B08.4 Enteroviral vesicular stomatitis with exanthema
B15.0 Hepatitis A with hepatic coma
B15.9 Hepatitis A without hepatic coma
B19.0 Unspecified viral hepatitis with hepatic coma
B19.9 Unspecified viral hepatitis without hepatic coma
B33.8 Other specified viral diseases
B34.1 Enterovirus infection, unspecified
B34.9 Viral infection, unspecified
B95.0 Streptococcus, group A, as the cause of diseases classified elsewhere

B95.1 Streptococcus, group B, as the cause of diseases classified elsewhere
B95.2 Enterococcus as the cause of diseases classified elsewhere
B95.3 Streptococcus pneumoniae as the cause of diseases classified elsewhere
B95.4 Other streptococcus as the cause of diseases classified elsewhere
B95.5 Unspecified streptococcus as the cause of diseases classified elsewhere
B95.6 Staphylococcus aureus as the cause of diseases classified elsewhere
B95.7 Other staphylococcus as the cause of diseases classified elsewhere
B95.8 Unspecified staphylococcus as the cause of diseases classified elsewhere
B96.1 Klebsiella pneumoniae [K. pneumoniae] as the cause of diseases classified elsewhere
B96.2 Escherichia coli [E. coli] as the cause of diseases classified elsewhere
B96.3 Hemophilus influenzae [H. influenzae] as the cause of diseases classified elsewhere
B96.4 Proteus (mirabilis) (morganii) as the cause of diseases classified elsewhere
B96.5 Pseudomonas (aeruginosa) (mallei) (pseudomallei) as the cause of diseases classified elsewhere
B96.6 Bacteroides fragilis [B. fragilis] as the cause of diseases classified elsewhere
B96.7 Clostridium perfringens [C. perfringens] as the cause of diseases classified elsewhere
B96.81 Helicobacter pylori [H. pylori] as the cause of diseases classified elsewhere
B96.82 Vibrio vulnificus as the cause of diseases classified elsewhere
B96.89 Other specified bacterial agents as the cause of diseases classified elsewhere
B97.0 Adenovirus as the cause of diseases classified elsewhere
B97.10 Unspecified enterovirus as the cause of diseases classified elsewhere
B97.11 Coxsackievirus as the cause of diseases classified elsewhere
B97.12 Echovirus as the cause of diseases classified elsewhere
B97.89 Other viral agents as the cause of diseases classified elsewhere
B99.8 Other and unspecified infectious diseases
B99.9 Unspecified infectious disease

K52.0 Gastroenteritis and colitis due to radiation
K52.1 Toxic gastroenteritis and colitis
K52.2 Allergic and dietetic gastroenteritis and colitis
K52.81 Eosinophilic gastritis or gastroenteritis
K52.82 Eosinophilic colitis
K52.89 Other specified noninfective gastroenteritis and colitis
K52.9 Noninfective gastroenteritis and colitis, unspecified

Z51.11: Encounter for antineoplastic chemotherapy (i.e. associated with chemotherapy-induced immunosuppression)

Thank you again for the opportunity to review and comment on this proposed policy. We respectfully ask that you consider these comments, which were prepared by experts including members of AGA, ASM, AMP, APHL, CAP, IDSA, and PASCV who provide services to Medicare beneficiaries covered by

Novitas Solutions. We are happy to be of assistance in providing additional clinical or other information to assist you with this draft LCD. Please direct your correspondence to Tara Burke, AMP Senior Director of Public Policy, at tburke@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Sincerely,

American Gastroenterological Association
American Society for Microbiology
Association for Molecular Pathology
Association of Public Health Laboratories
College of American Pathologists
Infectious Diseases Society of America
Pan American Society for Clinical Virology

References

1. Daniel-Wayman S, Fahle G, Palmore T, Green KY, Prevots DR Norovirus, astrovirus, and sapovirus among immunocompromised patients at a tertiary care research hospital 2018 92(2):143-146 https://doi.org/10.1016/j.diagmicrobio.2018.05.017
2. Kyne L, Warny M, Qamar A, Kelly CP. 2000. Asymptomatic carriage of Clostridium difficile and serum levels of IgG antibody against toxin A. N Engl J Med 342:390---397.
3. Leekha S, Aronhalt KC, Sloan LM, Patel R, Orenstein R. 2013. Asymptomatic Clostridium difficile colonization in a tertiary care hospital: admission prevalence and risk factors. Am J Infect Control 41:390---393.
4. Riddle MS, DuPont HL, Connor BA. ACG Clinical Guideline: diagnosis, treatment and prevention of acute diarrheal infections in adults. *Am J Gastroenterology*. 2016; 111:602-622.
5. Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, Langley JM, Wanke C, Warren CA, Cheng AC, Cantey J, Pikering LK 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea Clinical Infectious Diseases, Volume 65, Issue 12, 29 November 2017, Pages e45–e80, https://doi.org/10.1093/cid/cix669
6. Shim JK, Johnson S, Samore MH, Bliss DZ, Gerding DN. 1998. Primary symptomless colonisation by Clostridium difficile and decreased risk of subsequent diarrhea. Lancet 351:633---636.