August 14, 2017

Contractor Medical Director
Noridian Healthcare Solutions, LLC
JE Part A
Attention: Draft LCD Comments
PO Box 6781
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Re: MolDX: Multiplex Nucleic Acid Amplified Tests for Respiratory Viral Panels (DL37301)

Dear Dr. Lurvey,

The undersigned organizations appreciate the opportunity to review and comment on Noridian Healthcare Solution's Molecular Diagnostics (MolDx) Draft Local Coverage Determination ("dLCD") for Multiplex Nucleic Acid Amplified Tests for Respiratory Viral Panels (DL37301). The signatories to this letter include organizations whose members are experts in the diagnosis and treatment of respiratory conditions. This letter reflects the joint concerns of these organizations regarding Noridian's proposed non-coverage for multiplex PCR respiratory viral panels and, as such, we respectfully request that you consider these comments and recommendations outlined in this letter.

Coverage Indications, Limitations and/or Medical Necessity

We agree with Noridian that multiplex respiratory viral panel testing is not clinically indicated in all clinical scenarios. However, a global, non-coverage approach for multiplex PCR testing fails to recognize individual patient needs and can lead to a delay in treatment or ineffective treatment for many patients, particularly in elderly patients or those who are immunocompromised. **Therefore, we request that Noridian allow for coverage of these assays when they are determined to be clinically warranted, and especially in the three clinical scenarios detailed in this letter.**

Respiratory viruses are a common cause of community-acquired pneumonia (CAP)[4] and acute respiratory illness (ARI) in adults.[9] There is evidence and/or clinical practice guidelines to support the use of frontline multiplex PCR respiratory virus testing in three clinical ARI scenarios:
1) immunocompromised individuals, 2) adult patients with ARI in outpatient settings, and 3) select patients who are admitted to the intensive care unit (ICU), especially when the results are rapidly available allowing for timely patient management decisions to be made (e.g., antimicrobial treatment, hospital admission).

Nucleic acid amplification tests for the detection of viruses and atypical bacteria have been shown to improve the microbiologic diagnosis of CAP[12,22] compared to traditional, insensitive assays such as culture and antigen tests), especially in the elderly who shed lower titers of virus.[6,20]

Furthermore, there are no reliable clinical symptoms that allow for differentiation of the underlying heterogeneous pathogens that can cause CAP or polymicrobial infections, which can be caused by either viruses and/or bacteria.[10,16] The consensus clinical and diagnostic utility for these multiplex assays has recently been summarized in a comprehensive review.[25]

The following are clinical scenarios where multiplex respiratory viral panels are well documented to be clinically-warranted, and should thus be a covered Medicare benefit.

1. **Immunocompromised hosts.** A broad spectrum of respiratory pathogens can cause significant morbidity and mortality in adult and pediatric patients with a weakened immune system. There are several clinical scenarios where multiplex respiratory viral panels are well documented to be clinically-warranted, and should thus be a covered Medicare benefit. This is especially true for hematopoietic stem cell or solid organ transplant recipients, as well as for patients receiving high-dose chemotherapy and/or corticosteroids, biologics utilized for moderate/severe rheumatologic disorders (e.g., antitumor necrosis factor), and anti-lymphocyte agents and HIV. Early diagnosis is essential for optimal patient management (e.g., to direct antiviral therapy, to initiate or discontinue antibiotic therapy, to guide decisions about chemotherapy or timing of transplant,[19] and (although not a patient-specific Medicare benefit), for informing optimized hospital infection control practices. Current U.S. and international guidelines endorse upfront, simultaneous testing for multiple respiratory viruses (i.e., testing beyond influenza A/B and RSV only) in transplant and cancer patients.[5,8,13,24]

2. **Adult patients appearing acutely ill who are potential hospital admissions.** Two different studies evaluating rapid multiplex respiratory viral testing have shown the positive clinical impact of rapid, comprehensive multiplex panels relative to traditional testing[17] or individual molecular methods.[2] Access to rapid multiplex testing in the clinic or emergency department (ED), was associated with a decrease in unnecessary antibiotic use in both studies. Additionally, the study by Rappo et al., observed that ED length of stay, need for hospital admission, and number of chest radiographs were statistically reduced for patients with influenza who had a multiplex assay.[17] There is also a trend toward higher rates of discharge from the ED (without hospital admission) for patients that tested positive for non-influenza viruses. These studies are in agreement with a recent pediatric cost-effectiveness model that found rapid multiplex testing to be the most effective approach for evaluating ARIs in the ED.[15]

   To date, there is a single prospective randomized trial comparing rapid multiplex testing to routine clinical care for adults presenting to the ED.[1] Pre-specified secondary outcome assessments showed that patients in the group tested by a multiplex respiratory panel were statistically more likely to receive a single-dose or brief course of antibiotics, as well as have a shorter median length of hospital stay than the control group. Furthermore, more patients in the multiplex panel group were diagnosed and treated for influenza. Early detection and appropriate treatment of influenza could have resulted in reduced mortality and complications for hospitalized patients.[14]

3. **Critically-ill adult patients, particularly ICU patients.** Human metapneumovirus, parainfluenza viruses, rhinoviruses, and coronaviruses have all been associated with severe ARI in adult and elderly patients.[3,18] Furthermore, viral and bacterial co-infection has been linked to more severe CAP and longer hospitalization than those with a bacterial etiology alone.[11,23] Currently, the FDA-cleared multiplex panels are the only diagnostic option for many of these non-influenza viruses and atypical bacterial pathogens associated with CAP. Even though there are no proven antiviral therapies for the non-influenza viruses, the ability to make a diagnosis of an ARI in the ICU enhances the ability to reduce unnecessary antibiotic use, which is a major cause of morbidity in hospitalized patients.[21]

Other indirect benefits for diagnosing these viral infections include ending the “diagnostic odyssey”, allowing for the de-escalation of broad, empiric therapy,[7] and enhancing hospital infection prevention and prognosis efforts, which may impact the emergence of antimicrobial resistance.

The misuse of antibiotics, as when used inappropriately for viral infections, can lead to severe adverse effects in patients. A recent study by Tamma et al.,[21] demonstrated that a large proportion of hospitalized patients experience antibiotic-associated adverse effects. The authors drew several conclusions from this research, including that 20% of patients experienced one or more adverse effects and with each additional 10 days of antibiotics the adverse effects increased by 3%. It was also noted that 4% of patients developed Clostridium difficile infections, 6% of patients developed infections with multidrug-resistant organisms, and 24% of patients had prolonged hospital stays as a result of their adverse effects. In addition, the authors concluded that 19% of antibiotics prescribed in this study were unnecessary. Undoubtedly, some of the unnecessary antibiotic use reported in this study could have been reduced with timely multiplex respiratory virus testing.

ICD-10 Coding

Based on our above recommendations, we request that Noridian include the following additional ICD-10 coded indications in the final LCD. Many of these requested ICD-10 codes are clinically warranted due to the inability to clinically distinguish (with signs and symptoms) the various viral and/or bacterial causes of respiratory infections before doing the definitive diagnostic test.

ICD-10 Code	Descriptor
B34.1	Enterovirus
B34.8	Parainfluenza virus - rhinovirus
A37.01	Bordetella pertussis
B96.3	Haemophilus influenzae [H. influenzae] 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
B97.29	Other coronavirus as the cause of disease classified elsewhere
B97.89	Rhinovirus - as cause of disease classified elsewhere
J06.9	Acute Upper Respiratory Infection, unspecified
J09-J18	Influenza and Pneumonia
J10.00 - J10.89	Influenza due to other identified influenza virus
J11.00 - J11.89	Influenza due to unidentified influenza virus
J12	Viral pneumonia, not elsewhere classified
J12.0	Adenoviral pneumonia
J12.1	Respiratory syncytial virus pneumonia
J12.2	Parainfluenza virus
J12.3	Human metapneumovirus pneumonia
J13	Pneumonia due to streptococcus pneumoniae
J14	Pneumonia due to haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J15.0	Pneumonia due to Klebsiella pneumoniae
J15.1	Pneumonia due to pseudomonas
J15.212	Pneumonia due to methicillin resistant staphylococcus aureus
J15.4	Pneumonia due to other streptococci
J15.7	Pneumonia due to Mycoplasma pneumoniae
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J16.0	Chlamydial pneumonia
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, unspecified organism
J20.0	Acute bronchitis due to Mycoplasma pneumoniae
J20.1	Acute bronchitis due to Haemophilus influenzae

J20.3	Acute bronchitis due to coxsackievirus
J20.7	Acute bronchitis due to echovirus
J21.0	Acute bronchitis due to respiratory syncytial virus
J39.8	Other specified diseases of upper respiratory tract
Z94.1	Heart transplant status
Z94.2	Lung transplant status
Z94.4	Liver transplant status
Z94.81	Bone marrow transplant status
Z94.82	Intestine transplant status
Z94.83	Pancreas transplant status
Z94.84	Stem cells transplant status
Z94.89	Other transplanted organ and tissue status

Conclusion

We respectfully disagree with Noridian's conclusions that "the use of highly multiplexed NAAT tests as front-line diagnostics cannot be justified at the current time" and that these highly sensitive and specific FDA-approved tests do not meet Medicare's criteria for "reasonable and necessary" services. Disease severity can be especially high in the immunocompromised and elderly patient populations. Studies show that rapid identification of the causative agent(s) of respiratory tract infections is essential to provide an accurate diagnosis and appropriately manage patient care. It is also a key component in restricting antibiotic use to those circumstances in which antibiotic therapy is clearly indicated. Therefore, we urge Noridian to consider the evidence that we have presented in this letter and allow for coverage of these assays when documented as clinically necessary.

Thank you again for the opportunity to review and comment on this proposed policy. The undersigned organizations 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 Director of Public Policy, at tburke@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org.

Sincerely,

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

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