July 19, 2017

Palmetto GBA
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Re: MolDX: Multiplex Nucleic Acid Amplified Tests for Respiratory Viral Panels (DL37258)

Dear Dr. Almas and Dr. Jeter,

The Association of Public Health Laboratories (APHL) appreciates the opportunity to comment on the Palmetto Molecular Diagnostics (MolDx) Draft Local Coverage Determination ("dLCD") for Multiplex Nucleic Acid Amplified Tests for Respiratory Viral Panels (RVPs) (DL37258). APHL's membership comprises governmental public health laboratories who are experts in both diagnostic and surveillance testing for respiratory pathogens. While we recognize that Palmetto's proposed non-coverage decision is strictly a clinical testing reimbursement issue, we would like to take the opportunity to express our concerns about the impact on public health and clinical care. Additionally, we would like to clarify several public health issues that were cited in the decision rationale.

- **Clinical and Seasonal Overlap of Respiratory Viruses:** To clarify the proposal's assertion that diagnosis can be made by a clinician on the basis of seasonality and clinical symptoms, as public health practitioners, our individual state laboratory-based surveillance systems for respiratory illnesses provide ample evidence that many of the viruses included in these panels share symptoms and overlap in seasonality. These findings are supported by studies in the U.S. and abroad.[1,2,3,4]
- **Utility in Outbreak Situations for Patient Care:** During outbreaks, multiplex panels fill an important role in clinical decisions by ruling in other etiologies and providing reassurance in a rapid manner to clinicians, patients, families and public health officials. As currently written, this proposal oversimplifies the clinical manifestations of these viruses and ignores the value of determining a specific etiology of a disease that cannot be determined from direct testing for influenza and RSV alone. This additional information is crucial in tailoring pathogen specific intervention and prevention efforts.
- **Unusual Clinical Presentations:** The multiplex panel is also useful when unexpected disease activity occurs. For example, HIV infection in the acute phase often presents as an influenza-like-illness. However, if the initial clinical suspicion is wrong and tests are negative for respiratory viruses, this allows clinicians to have further conversations with their patients to determine if an HIV test is indicated. Without the multiplex panel ruling out other viruses, this delays a healthcare provider's ability to determine a diagnosis. Respiratory virus panels save time and

resources and ultimately lead to a faster public health intervention and prevent transmission to other people.[5]

Another example of the utility of respiratory pathogen multiplex panels occurred during 2014-2015 when over 300 patients across multiple states presented with parotitis and symptoms similar to mumps in the winter months, though all tested negative for mumps. Molecular testing, including the use of a respiratory virus panel, led to the detection of influenza and several other respiratory viruses in over 70% of these patients and revealed that the circulating influenza A H3 subtype that year could cause rare parotitis symptoms. Respiratory virus panels can be very important for patient management decisions especially when there are other viral pathogens known to cause similar symptoms. By using a broad panel for diagnosis, clinical decisions are made in an effective and efficient manner.

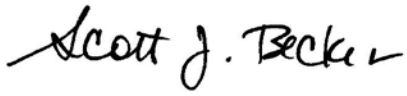
- **Traveler Diagnosis:** Palmetto should not disregard the utility of these panels in case of traveler illness and novel disease detection. These panels can be conducted in parallel when ruling out pathogens of high consequence. For example, a physician may request a respiratory virus panel on all MERS-CoV rule outs in parallel to MERS-CoV testing because time is critical when ruling in another etiology if the MERS-CoV test is negative. Being able to provide an alternative answer gives more confidence to the physician, public health officials and patient in a negative result for a pathogen of high consequence.
- **Assay Performance:** While further data would be useful on these panels, particularly for sensitivity for different pathogens, the assays have demonstrated reliable positive predictive values. Furthermore, these assays are far superior to rapid antigen detection assays and timelier than culture, which many laboratories no longer maintain for respiratory pathogens.
- **Impact on Public Health Affects Clinical Care and Patient Management**: While APHL recognizes that reimbursement should not occur for the sake of public health surveillance testing, the clinical laboratory data collected from these panels serve as the foundation for many state and federal respiratory surveillance reports. The healthcare system relies on these surveillance reports to make informed clinical judgments for patient care. Knowledge of which pathogens are currently circulating helps physicians in their differential diagnosis. The proposal will likely have a negative impact on state and federal public health surveillance systems and will diminish the amount of data available to physicians, ultimately compromising the quality of patient care.

Recognizing that the use of these panels not only benefits individual patients, but also public health, APHL proposes that reimbursement be changed to a per panel basis rather than per pathogen basis. Alternately, Palmetto should consider reimbursing only for a universal core set of pathogens that have clinical and seasonality overlap, including the following:

- Adenovirus
- Coronaviruses
- Human metapneumovirus
- Influenza viruses
- RSV
- Parainfluenza viruses
- Human rhinovirus/enteroviruses

APHL urges Palmetto to consider the public health impact when making local coverage determinations concerning pathogens of public health significance. For more information, please contact Celia Hagan, Manager, Public Policy at celia.hagan@aphl.org.

Sincerely,



Scott Becker, MS
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APHL works to strengthen laboratory systems serving the public's health in the U.S. and globally. APHL's member laboratories protect the public's health by monitoring and detecting infectious and foodborne diseases, environmental contaminants, terrorist agents, genetic disorders in newborns and other diverse health threats.

References:

1. Drinka, Paul J., Stefan Gravenstein, Peggy Krause, Elizabeth H. Hanger, Lori Barthels, Margaret Dissing, Peter Shult, and Margo Schilling. "Non-Influenza Respiratory Viruses May Overlap and Obscure Influenza Activity." Journal of the American Geriatrics Society 47.9 (1999): 1087-093.
2. Radin, Jennifer M., Anthony W. Hawksworth, Peter E. Kammerer, Melinda Balansay, Rema Raman, Suzanne P. Lindsay, and Gary T. Brice. "Epidemiology of Pathogen-Specific Respiratory Infections among Three US Populations." PLoS ONE 9.12 (2014)
3. Olofsson, Sigvard, Robin Brittain-Long, Lars Magnus Andersson, Johan Westin, and Magnus Lindh. "PCR for detection of respiratory viruses: seasonal variations of virus infections." Expert Review of Anti-infective Therapy 9.8 (2011): 615-26.
4. Lamson, Daryl, Neil Renwick, Vishal Kapoor, Zhiqiang Liu, Gustavo Palacios, Jingyue Ju, Amy Dean, Kirsten St. George, Thomas Briese, and W. Ian Lipkin. "MassTag Polymerase-Chain-Reaction Detection of Respiratory Pathogens, Including a New Rhinovirus Genotype, That Caused Influenza-Like Illness in New York State during 2004–2005." The Journal of Infectious Diseases 194.10 (2006): 1398-402.
5. Centers for Disease Control and Prevention: HIV/AIDS https://www.cdc.gov/hiv/basics/whatishiv.html