Clinical UM Guideline

Subject:	Respiratory Viral Panel Testing in the Outpatient Setting		
Guideline #:	CG-LAB-14	**Publish Date:**	09/25/2019
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Description

This document addresses the use of respiratory viral panel (RVP) testing in the outpatient setting. RVPs are multiplexed nucleic acid tests used to detect respiratory viruses including, but not limited to: adenovirus, coronavirus (229E, HKU1, NL63, OC43), human bocavirus, human metapneumovirus, human rhinovirus/enterovirus, influenza A (A, H1, H1-2009, H3), influenza B, parainfluenza (1, 2, 3, 4), respiratory syncytial virus (A, B). This document does not address RVP testing in the inpatient setting.

Note: Please see the following related document for additional information:

- ADMIN.00007 Immunizations

Clinical Indications

Medically Necessary:

Respiratory viral panel testing in the outpatient setting is considered **medically necessary** for individuals who are at high risk for complications of respiratory viral infection, including but not limited to individuals who are immunocompromised, including lung transplant recipients, when the result of testing is used to guide or alter management.

Not Medically Necessary:

Respiratory viral panel testing in the outpatient setting is considered **not medically necessary** for average risk individuals and for individuals who are not at high risk of complications and for whom the result of testing is unlikely to guide management.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT

87631	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types of subtypes, 3-5 targets
87632	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types of subtypes, 6-11 targets
87633	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types of subtypes, 12-25 targets
0098U	Respiratory pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes, 14 targets (adenovirus, coronavirus, human metapneumovirus, influenza A, influenza A subtype H1, influenza A subtype H3, influenza A subtype H1-2009, influenza B, parainfluenza virus, human rhinovirus/enterovirus, respiratory syncytial virus, Bordetella pertussis, Chlamydophila pneumoniae, Mycoplasma pneumoniae) BioFire® FilmArray® Respiratory Panel (RP) EZ, BioFire® Diagnostics
0099U	Respiratory pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes, 20 targets (adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus, coronavirus OC43, human metapneumovirus, influenza A, influenza A subtype, influenza A subtype H3, influenza A subtype H1-2009, influenza, parainfluenza virus, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 4, human rhinovirus/enterovirus, respiratory syncytial virus, Bordetella pertussis, Chlamydophila pneumonia, Mycoplasma pneumoniae) BioFire® FilmArray® Respiratory Panel (RP), BioFire® Diagnostics
0100U	Respiratory pathogen, multiplex reverse transcription and multiplex amplified probe technique, multiple types or subtypes, 21 targets (adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus NL63, coronavirus OC43, human metapneumovirus, human rhinovirus/enterovirus, influenza A, including subtypes H1, H1-2009, and H3, influenza B, parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 4, respiratory syncytial virus, Bordetella parapertussis [IS1001], Bordetella pertussis [ptxP], Chlamydia pneumoniae, Mycoplasma pneumoniae) BioFire® FilmArray® Respiratory Panel 2 (RP2), BioFire® Diagnostics
0115U	Respiratory infectious agent detection by nucleic acid (DNA and RNA), 18 viral types and subtypes and 2 bacterial targets, amplified probe technique, including multiplex reverse transcription for RNA targets, each analyte reported as detected or not detected

ePlex Respiratory Pathogen (RP) Panel, GenMark Diagnostics, Inc, GenMark Diagnostics, Inc

ICD-10 Diagnosis

All diagnoses

Discussion/General Information

RVPs are multiplexed nucleic acid tests used for the simultaneous detection of respiratory pathogens. Examples of these respiratory pathogens include adenovirus, coronavirus (229E, HKU1, NL63, OC43), human bocavirus, human metapneumovirus, human rhinovirus/enterovirus, influenza A (A, H1, H1-2009, H3), influenza B, parainfluenza (1, 2, 3, 4), and respiratory syncytial virus (A, B). The panels vary based on the extent of multiplexing (4 to 22 targets), level of the method (moderate to high), throughput (low to high), and time to results (less than 1 hour to 8 hours). Effective antiviral agents are available for certain respiratory viruses (for example, influenza) but not for others. Results of these panels may be used in the inpatient setting to aid in decisions regarding discontinuation of RSV prevention [Synagis® (palivizumab) prophylaxis; AstraZeneca, Cambridge, United Kingdom], initiation or continuation/discontinuation of antibiotic therapy, anti-influenza therapy, or isolation or cohorting of hospitalized individuals.

High Risk Individuals

Studies evaluating the use of RVP testing in the outpatient setting have generally been limited to high risk populations, for example, immunocompromised individuals, including lung transplant recipients. Respiratory viral infections can cause significant morbidity and mortality in high risk populations (Bridevaux, 2014; Fisher, 2016; Gottlieb, 2009; Kumar, 2012; Magnusson, 2013; Soccal, 2010). In conditions such as lung transplantation, infections with respiratory viruses are a common and potentially serious complication, and often present with nonspecific clinical findings; furthermore, management strategies vary depending on the specific virus causing the infection. As reported in a surveillance study conducted by Kumar and colleagues (2010), respiratory viral infections are commonly detected in bronchoalveolar lavages (BAL) obtained from lung transplant individuals. After BAL samples collected from 93 lung transplant individuals underwent RVP testing using the xTAG® Respiratory Viral Panel (Luminex Corporation, Austin, TX), the authors found that "biopsy-proven acute rejection (≥ grade 2) or decline in forced expiratory volume in 1 sec ≥20% occurred in 16 of 48 (33.3%) patients within 3 months of RVI when compared with 3 of 45 (6.7%) RVI-negative patients within a comparable time frame (p=0.001)" (Kumar, 2010). While it's acknowledge further studies are needed, the authors postulated that since asymptomatic or symptomatic respiratory viral infections can trigger acute rejection, RVP testing may help with clinical disease management in lung transplant individuals.

As noted in a retrospective study (Hammond 2012), timely diagnosis is recommended for rapid care in high risk populations to help with clinical disease management. In an effort to identify a diagnostic test with a faster turnaround time than conventional methods, Hammond and colleagues evaluated the performance of the FilmArray® Respiratory Panel EZ (RP EZ) (bioMérieux, Inc., Marcy-l'Étoile, France) as compared to standard

clinical testing in immunocompromised individuals (n=87). Through verification with real-time PCR, the evaluators found that the FilmArray assay identified significantly more respiratory viral pathogens than standard clinical testing (p=0.001), and concluded that it can provide rapid and accurate diagnosis in immunocompromised individuals, which is critical for clinical disease management.

Antibiotic Stewardship in Average Risk Individuals in the Outpatient Setting

While RVP testing for antibiotic stewardship has been evaluated in average risk individuals in the outpatient setting, as described below, the evidence lacks clinical utility.

Doan and colleagues (2009) published a randomized controlled trial with the aim to evaluate the rate of ancillary testing and antibiotic prescription rate in pediatric cases in the emergency department (ED). Using a computer randomization program, individuals were randomly assigned to received RVP testing (n=90) or nasopharyngeal washing for rapid viral diagnostic test (n=110). The authors did not find a statistically significant difference in rate of ancillary testing [(chest X-ray: RR 0.86; 95% confidence interval [CI], 0.44, 1.11), (blood work: RR 0.59; 95% CI, 0.28, 1.23), (urine analysis: RR 1.12; 95% CI, 0.73, 1.71)] or antibiotic prescription rate (RR 0.86; 95% CI, 0.48, 1.53) in the ED.

In 2011, Brittain-Long and colleagues performed a multicenter, open-label, randomized control trial to assess the impact of RVP testing on antibiotic prescription rates in adult individuals. RVP testing was performed on all individuals who were then randomized into the rapid results cohort (n= 202) or the delayed result cohort (n= 204). Based on randomization, the treating physician received the results from the RVP testing either on the day following inclusion (the rapid result cohort) or 8 to 12 days later (the delayed result cohort). The results showed 4.5% of individuals in the rapid results cohort received antibiotics at the initial visit compared to 12.3% of individuals in the delayed result cohort (p=0.005); however, there was no significant difference between the two groups at the follow-up visit (10 days post-initial visit) [13.9% in the rapid result group and 17.2% in the delayed result group (p=0.359)]. Further research is needed to identify how to sustain the initial results.

In 2016, Green and colleagues also evaluated the impact of RVP testing on antibiotic prescription rates in adult individuals (n=295) through a retrospective chart review. Individuals' charts were evaluated based on three test groups: tested positive for influenza virus (n=105), tested positive for a non-influenza virus pathogen (n=109), and no respiratory pathogen detected (n=81). The authors found a significant difference in rates of oseltamivir (p<0.0001) and antibiotic prescriptions (p=0.005) among the three groups; however, there was no significant difference in antibiotic prescription rates between the non-influenza virus pathogen group and the no respiratory pathogen detected group (p=1.0). The authors concluded that "testing positive for influenza virus was associated with receiving fewer antibiotic prescriptions, but no such effect was seen for those who tested positive for a non-influenza virus. These data suggest that testing for influenza viruses alone may be sufficient" (Green, 2016).

Echavarría and colleagues (2018) published the results of a prospective, randomized, non-blinded study that assessed the impact of RVP testing on antibiotic and antiviral prescription, and use of complementary studies (chest x-ray, computerized tomography scan, complete blood count, urinary antigen for *Streptococcus pneumoniae* or

Legionella pneumoniae, and bacterial cultures of blood, urine or sputum). During the 2016 and 2017 respiratory seasons (April-November 2016 and April-October 2017), 432 individuals (156 children and 276 adults) who presented to a single center emergency department with signs and symptoms of an acute lower respiratory infection had testing performed via the FilmArray assay (n=289) or immunofluorescence assay (IFA) (n=143). High risk individuals, such as those with cancer, HIV, immunosuppression, or organ transplants, were excluded from the study. The results showed a change in medical management was significantly more likely in the FilmArray assay group than the IFA group in both children (odds ratio [OR]=8.07; CI 95% 3.03–21.47; $p < 0.001$) and adults (OR=2.67; CI 95% 1.32–5.40; p=0.006). For antibiotics, a significant change in treatment plan was observed in both children (OR=12.23; CI 95% 1.56–96.09; p=0.017) and adults (OR=15.52; CI 95% 1.99–120.83; p=0.009) in the FilmArray assay group versus the IFA group. While there were significant changes noted in antiviral prescription for both FluA/B positive adults (p=0.091) and FluA/B negative adults (p=0.042), there was no significant change in antiviral prescription noted in children between the two study groups. As for complementary studies, there was a significant decrease of usage noted in children between the two groups (p=0.001); however, a significant change was not noted in adults. While this study has some positive findings, more studies are needed to validate these results in the average risk population.

Sensitivity, Specificity, and Predictive Value

RVP can replace conventional methods such as viral culture and direct florescent antibody testing. Multiple studies have demonstrated that multiplex PCR provides greater yield and sensitivity than conventional methods in immunocompromised individuals, including lung transplant recipients (Gottlieb, 2009; Hopkins, 2003; Kumar, 2005; Weinberg, 2002).

Gadsby and colleagues (2010) reported on a retrospective study that compared the xTAG® Respiratory Viral Panel FAST (Luminex Corporation, Austin, TX), commonly known as the RVP Fast assay, with viral culture, a direct fluorescent assay (DFA), and a panel of single and multiplex real-time PCRs in the testing of 286 respiratory specimens. The sensitivity and specificity of the RVP Fast assay compared to the multiplex real-time PCR were 78.8% and 99.6%, respectively; however the sample set used had a low number of specimens that were not positive for several of viruses, such as influenza and parainfluenza. More studies are needed with larger numbers of positive specimens to properly assess the RVP Fast assay.

In 2017, Chiu and colleagues published a prospective study with the aim to compare FilmArray assay to cell culture and PCR. A total of 60 samples were collected from November 2016 to January 2017. Of the 60 samples, 52 tested positive for respiratory pathogens. While the FilmArray assay showed higher sensitivity than PCR and a positive predictive value of 100%, the results of the FilmArray assay and cell culture were identical. In addition, the study did not evaluate clinical utility of the FilmArray assay.

Summary

At this time, the evidence supporting RVP testing in the outpatient setting is limited to individuals who are at high risk for complications of respiratory viral infection, including immunocompromised individuals as well as

including lung transplant recipients, when the result of testing is used to guide or alter management. Evidence does not demonstrate clinical utility in average risk individuals; use of these tests have not been shown to change treatment decisions and improve subsequent clinical outcomes.

Definitions

Antibiotic stewardship: Coordinated efforts designed to optimize treatment of infections and reduce adverse events associated with antibiotic use.

Multiplexed nucleic acid test: Simultaneous detection of DNA or RNA to determine the presence of one or more viruses in a specimen.

References

Peer Reviewed Publications:

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2. Bridevaux PO, Aubert JD, Soccal PM, et al. Incidence and outcomes of respiratory viral infections in lung transplant recipients: a prospective study. Thorax. 2014; 69(1):32-8.
3. Brittain-Long R, Westin J, Olofsson S, et al. Access to a polymerase chain reaction assay method targeting 13 respiratory viruses can reduce antibiotics: a randomised, controlled trial. BMC Med. 2011; 9:44.
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5. Doan QH, Kissoon N, Dobson S, et al. A randomized, controlled trial of the impact of early and rapid diagnosis of viral infections in children brought to an emergency department with febrile respiratory tract illnesses. J Pediatr. 2009; 154(1):91-95.
6. Echavarría M, Marcone DN, Querci M, et al. Clinical impact of rapid molecular detection of respiratory pathogens in patients with acute respiratory infection. J Clin Virol. 2018; 108:90-95.
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8. Gadsby NJ, Hardie A, Claas EC, et al. Comparison of the luminex respiratory virus panel fast assay with in-house real-time PCR for respiratory viral infection diagnosis. J Clin Microbiol. 2010; 48(6):2213-2216.
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12. Hopkins PM, Plit ML, Carter IW, et al. Indirect fluorescent antibody testing of nasopharyngeal swabs for influenza diagnosis in lung transplant recipients. J Heart Lung Transplant. 2003; 22(2):161-168.
13. Kumar D, Erdman D, Keshavjee S, et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transplant. 2005; 5(8):2031-2036.
14. Kumar D, Husain S, Chen MH, et al. A prospective molecular surveillance study evaluating the clinical impact of community-acquired respiratory viruses in lung transplant recipients. Transplantation. 2010; 89(8):1028-33.
15. Magnusson J, Westin J, Andersson LM, et al. The impact of viral respiratory tract infections on long-term morbidity and mortality following lung transplantation: a retrospective cohort study using a multiplex PCR panel. Transplantation. 2013; 95(2):383-388.
16. Soccal PM, Aubert JD, Bridevaux PO, et al. Upper and lower respiratory tract viral infections and acute graft rejection in lung transplant recipients. Clin Infect Dis. 2010; 51(2):163-170.
17. Weinberg A, Zamora MR, Li S, et al. The value of polymerase chain reaction for the diagnosis of viral respiratory tract infections in lung transplant recipients. J Clin Virol. 2002; 25(2):171-175.

Websites for Additional Information

1. Centers for Disease Control and Prevention (CDC). Available at: https://www.cdc.gov/. Accessed on July 5, 2019.
    - About Adenoviruses. Last reviewed: April 26, 2018.
    - Common Colds: Protect Yourself and Others. Last reviewed: February 11, 2019.
    - About Coronaviruses. Last reviewed: November 9, 2017.
    - Human Metapneumovirus (HMPV) Clinical Features. Last reviewed: May 14, 2019.
    - About Human Parainfluenza Viruses (HPIVs). Last reviewed: October 6, 2017.
    - Influenza (Flu). Last reviewed: June 11, 2019.
    - About RSV. Last reviewed: June 26, 2018.
2. National Institutes of Health (NIH). Available at: https://www.nih.gov/. Accessed on July 5, 2019.
    - Influenza. Last reviewed: July 13, 2017.
    - Parainfluenza Virus Type 3. Last updated: August 30, 2016.
    - Respiratory Syncytial Virus (RSV). Last reviewed: December 12, 2008.

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ePlex® (GenMark Diagnostics, Inc., Carlsbad, CA)
FilmArray Respiratory Panel EZ (RP EZ)
NxTAG® Respiratory Pathogen Panel (Luminex Corporation, Austin, TX)
VERIGENE® Respiratory Pathogens Flex Test (Luminex Corporation, Austin, TX)
xTAG® Respiratory Viral Panel
xTAG Respiratory Viral Panel FAST

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	08/22/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Discussion/General Information, References, and Websites for Additional Information sections. Updated Coding section with 10/01/2019 CPT changes; added 0115U.
	06/27/2019	Updated Coding section with 07/01/2019 CPT changes; added 0098U-0100U.
New	11/08/2018	MPTAC review. Initial document development.