Respiratory Pathogen Nucleic Acid Detection Testing

Policy Number: 2025T0661A
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➲ Instructions for Use

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Related Commercial Policies
None

Coverage Rationale

Respiratory pathogen panel testing of six or more targets in an outpatient setting is unproven and not medically necessary due to insufficient evidence of efficacy for all indications.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
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
0202U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab, each pathogen reported as detected or not detected
0223U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab, each pathogen reported as detected or not detected
0225U	Infectious disease (bacterial or viral respiratory tract infection) pathogen-specific DNA and RNA, 21 targets, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), amplified probe technique, including multiplex reverse transcription for RNA targets, each analyte reported as detected or not detected
87632	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (e.g., adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets

CPT Code	Description
87633	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (e.g., adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets

Description of Services

Acute respiratory infections (ARIs) are a major global health concern, significantly contributing to illness and death across the world. While these infections tend to be more severe in vulnerable groups such as children, the elderly, and individuals with weakened immune systems, they can affect people of all ages and demographics. The widespread nature of ARIs leads to a substantial burden on healthcare systems, evidenced by increased visits to medical offices and emergency departments, a higher number of antimicrobial prescriptions, and a rise in hospital admissions. Additionally, ARIs result in considerable lost productivity due to missed work and school days (Echavarría et al. 2018). Most of these infections are caused by viruses, though bacteria and other organisms can also be. The range of causative agents keeps growing as new pathogens and syndromes are identified. The latest addition is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which triggered the ongoing global pandemic that started in 2019.

Respiratory pathogen panel testing may detect multiple pathogens simultaneously, including bacterium, viruses, and fungi, as well as antibiotic-resistance genes from a single specimen. Several manufacturers have now developed these respiratory pathogen panels that include nucleic acid amplification tests (NAATs) and panel assays using Polymerase Chain Reaction (PCR) which have the ability to produce results more quickly compared to that of the traditional methods like viral culture, serologies, and direct fluorescence antibody staining which are limited by slow turnaround times and sensitivity.

Clinical Evidence

There is insufficient evidence to support the use of respiratory pathogen panel testing of six or more targets in an outpatient setting due to insufficient evidence of efficacy. The fixed nature of these larger multiplex panels includes pathogens that cause infections different enough that simultaneous testing for these pathogens should be rare. The results must be interpreted in light of prolonged shedding periods, the possibility of multiple positive results or coinfections and variable accuracy for different agents on the panels The quality of the studies was low due to small study populations, short follow-up, and lack of randomization and appropriate control groups. Further studies are needed to confirm its clinical utility related to management and improved individual outcomes.

Gripp et al. (2023) conducted a retrospective chart review of respiratory pathogen panels (RPPs) in outpatient oncology patients with respiratory tract infection (RTI) symptoms from April 2020 to November 2021. A prior study by Green et al. (2016) (included below) indicated that RRPs are not recommended for routine use in healthy adult outpatients presenting with RTI and influenza testing alone has been found to have similar outcomes. Of the 183 RPPs analyzed in this study, 31 (16.9%) were positive for at least 1 respiratory virus. Eighteen (54.5%) were positive for *human rhinovirus/enterovirus*, 9 (27.2%) for *parainfluenza virus* 3, 2 (6.1%) for *para1influenza virus* 4, and one each (3.0%) for RSV A, RSV B, *coronavirus* OC43, and *human metapneumovirus*. Two patients had RPP positive for 2 viruses. Despite this, only 1.6% of patients had changes in their medication based on RPP results. Antibiotics were prescribed to 28.4% of patients before RPP results, with minimal adjustments afterward. No antiviral medications were started before RPP results, and only one patient began antiviral therapy post-results. The study suggests targeted testing for specific viruses like influenza, RSV, and SARS-CoV-2 may be more appropriate. Study limitations include the following: retrospective design with variation in documentation of symptoms, exam findings and follow up care; small sample size, lack of a comparison group of patients who did not receive an RPP when presenting with RTI symptoms; minimal influenza during the 2020–2021 season. The authors noted that in this cohort of oncology patients presenting to a large academic center with symptoms of RTI, RPP use did not appear to impact clinical management. Further studies are needed to validate the clinical utility of RPPs in outpatient settings.

In a 2023 Molecular Test Assessment, Hayes found the FilmArray RP2 test aims to detect multiple respiratory pathogens from nasopharyngeal swabs to help diagnose respiratory infections. However, there is insufficient evidence to support its use, primarily due to limited data on its effectiveness. (Hayes, FilmArray Respiratory Panel 2 [BioFire Diagnostics LLC], 2023).

In 2023, Hayes published a review on the BioFire FilmArray Respiratory Panel (RP), assessing its analytical and clinical validity, as well as its clinical utility. The review included 16 studies: nine on performance, eight on run and turnaround times, and one on detection limits. Four studies focused on nasopharyngeal swabs, showing good agreement with other nucleic acid amplification tests (NAATs) and good sensitivity and specificity for certain pathogens, though some cross-reactivity was noted.

The review found that while the FilmArray RP might improve therapeutic management, evidence on clinical outcomes like reduced hospital stays and better antibiotic prescription rates was conflicting. The authors concluded that the evidence supporting the use of the FilmArray RP for detecting multiple respiratory pathogens in nasopharyngeal swabs is of low quality. This is due to limited data on test accuracy and a lack of comprehensive clinical validity studies. While the test shows similar performance to other detection methods, further studies are needed to confirm its accuracy and impact on patient outcomes. (Hayes, FilmArray Respiratory Panel [BioFire Diagnostics LLC], 2023)

Murphy et al. (2020) in a multicenter study evaluated the performance of BioFire FilmArray Pneumonia Panel (PN panel) and Pneumonia Plus Panel (PNplus panel) against the traditional diagnostic methods like culture, molecular testing, and antigen detection to improve individual outcomes and support antimicrobial stewardship. The traditional methods often require multiple specimen types, extensive processing, and can have low sensitivity and long turnaround times. The PN panel and the PNplus panel are FDA-cleared assays that detect viruses, atypical bacteria, bacteria, and antimicrobial resistance genes from sputum and bronchoalveolar lavage (BAL) fluid. The panels also provide semiquantitative results for bacterial targets. The paper details analytical and clinical studies conducted for regulatory clearance. It involved 846 BAL and 836 sputum specimens, which were also evaluated using quantitative reference culture and molecular methods for comparison. The PN panel demonstrated 100% sensitivity for 15 out of 22 targets in BAL specimens and 10 out of 24 in sputum specimens. Other targets had sensitivities of at least 75% or could not be calculated due to low prevalence. Specificity for all targets was at least 87.2%, with many false positives confirmed by alternative molecular methods. Limitations include the following: the panels' high sensitivity and specificity do not always align perfectly with traditional culture methods, with sensitivity for individual bacteria ranging from 46% to 100% and specificity from 61% to 100%; the semiquantitative results may not match the quantitative values from cultures, complicating the interpretation of the clinical significance of detected pathogens; the detection of a pathogen does not always indicate an active infection, as some organisms might be colonizers rather than true pathogens, complicating clinical decisions; and the accuracy of results can be affected by the quality of the respiratory specimen, with poor-quality specimens potentially giving inconclusive or difficult-to-interpret results. In conclusion, current pneumonia diagnosis algorithms use multiple methods. Molecular methods are commonly used for viral agents and atypical bacteria, while culture remains the gold standard for bacterial pneumonia diagnosis. Implementing the PN panel requires careful consideration of its use in specific individual populations, but it has the potential to significantly aid in individual management decisions. Further research is needed to fully establish the clinical utility of these panel tests.

Echavarría et al. (2018) conducted a prospective, randomized, non-blinded study that assessed the impact of multiplex panel testing and how the timely etiological identification would have an impact on the use of antibiotic and antiviral as well as 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, 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 distinguished in adults. Limitations included that this was a single center study and 1:1 randomized enrollment during the second portion of 2016 was not maintained. While this study has some positive findings, additional studies are needed to validate these results in the average risk population.

Kaku et al. (2018) in a prospective observational study aimed to evaluate the effectiveness of the FilmArray Respiratory Panel (RP) and to see if detecting viruses would aid in decreasing inappropriate prescriptions of antibiotics which could lead to antibiotic resistance. Even though viruses are typically the main cause of upper respiratory tract infections (URTI) and acute bronchitis, antibiotics are frequently prescribed. This study was conducted during an influenza epidemic and involved adult outpatients with respiratory tract infection symptoms at a hospital. The goal was to evaluate the

effectiveness of the FilmArray Respiratory Panel (RP). The study enrolled 50 patients, and the FilmArray RP identified pathogens in 28 of them. The most common pathogens found were influenza virus (14 cases), respiratory syncytial virus (6 cases), and human rhinovirus (6 cases). Interestingly, 6 out of the 14 patients with influenza virus tested negative on the antigen test. Physicians diagnosed and treated patients without the FilmArray RP results. Among the patients who tested positive with FilmArray RP, 9 received antibiotic treatment, but bacteria were found in only 3 of them. Study limitations included the following: small sample size which limited the generalizability of the results; samples were obtained during influenza epidemic; and lastly, there is a risk of false positives and negatives, impacting clinical decision-making. The authors note that the actual impact of FilmArray RP on URTI infection was not determined. Additional research is needed on the FilmArray RP to determine its efficiency and reliability, ultimately enhancing its clinical utility in diagnosing respiratory infections and improving patient care.

Ramanan et al. (2017) reviewed the literature on FDA-approved multiplex molecular panels in clinical microbiology, focusing on respiratory tract infections as well as other infectious diseases. They identified several limitations of these panels, such as the lack of customized ordering options, which can lead to unnecessary testing. The clinical significance of detecting multiple targets remains unclear, with studies showing a 10% coinfection rate, often involving enterovirus and rhinovirus, possibly due to cross-reactivity. Positive results may not distinguish between colonization and active infection and might miss bacterial or fungal coinfections. While these assays can provide diagnostic closure for clinicians and patients, potentially avoiding further testing, they may also diagnose infections that are typically missed due to lack of clinical suspicion or routine testing. Immunocompromised patients might benefit from these panels, whereas healthy individuals with mild infections might need more targeted or no testing. However, prolonged shedding of microorganisms in immunocompromised patients can complicate interpretation. Therefore, laboratory results should be interpreted in the context of clinical findings, and individualized guidelines for specific patient populations are necessary for proper use of these assays. Additional research is needed to establish a standard to determine the appropriate targets based on the individual's clinical presentation to aid in the clinical utility of these tests.

Green et al. (2016) conducted a retrospective review to evaluate if the results of multiplex PCR testing affect outcome measures among adult outpatients, especially those related to therapeutic management. Multiplex tests for respiratory infections can detect up to 20 common pathogens, mainly viruses. For those testing positive for influenza, oseltamivir is a specific treatment. Identifying non-influenza viruses can help avoid unnecessary antibiotic use. The authors analyzed antimicrobial prescriptions following respiratory pathogen testing among outpatients at a large Veterans Administration (VA) medical center. The study reviewed results from the FilmArray respiratory panel (BioFire, Salt Lake City, UT) for 408 outpatients between December 2014, and April 2015, along with their medical records. They examined differences in antibiotic and oseltamivir prescription rates. Out of 408 patients tested in various outpatient settings (emergency departments, urgent care clinics, and outpatient clinics), 295 (72.3%) were managed as outpatients. Among these 295 outpatients, 105 (35.6%) tested positive for influenza, 109 (36.9%) for a non-influenza virus, and 81 (27.5%) had no respiratory pathogen detected. There were significant differences in oseltamivir and antibiotic prescription rates among the three groups (chi-squared values of 167.6 [$p < 0.0001$] and 10.48 [$p = 0.005$], respectively). However, there was no significant difference in antibiotic prescription rates between the non-influenza virus group and those who tested negative (chi-square value, 0; $p = 1.0$). Study limitations included a single center study, multiplex tests did not test all pathogens, and positive results may not always be clinically relevant. The authors established 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. The additional benefit of performing multiplex virus testing instead of targeted influenza virus testing in outpatients is questionable, additional studies are needed.

Clinical Practice Guidelines

American Society for Microbiology (ASM)

In an ASM-sponsored Practical Guidance for Clinical Microbiology (PGCM) that identifies the best practices for diagnosis and characterization of viruses that cause acute respiratory infections (ARIs). The guidelines identified patient groups suitable for multiplexed respiratory viral panel testing. Testing needs can differ based on the patient environment and available resources, given the high costs of multiplex assays. The ideal candidates for testing may vary by healthcare setting, as some research questions the benefit of testing adult outpatients for viruses other than influenza.

- Hematology and oncology patients may be appropriate patient populations for testing.
- Transplant patients may also be an appropriate patient population for multiplex testing.
- Intensive care unit (ICU) patients may be another appropriate patient population for respiratory viral multiplex panel testing.
- Pediatric patients with an underlying illness may also be an appropriate patient population for respiratory viral panel testing.

(Charlton et al. 2018)

American Thoracic Society (ATS)

The key recommendations from the guideline on nucleic acid-based testing for non-influenza viral pathogens in adults with suspected community-acquired pneumonia (CAP). The guideline notes that routine NAA testing for non-influenza viruses has not shown significant impact on critical outcomes such as overall survival or antibiotic use patterns. The guideline highlights the need for further research to better understand the role of NAA testing in improving clinical outcomes for patients with CAP (Evans et al. 2021).

- For outpatients and immunocompetent inpatients with non-severe suspected CAP, the guideline conditionally recommends against routine nucleic acid amplification (NAA) testing for non-influenza respiratory pathogens.
- For hospitalized patients with severe CAP or those who are immunocompromised, the guideline suggests considering NAA testing for non-influenza respiratory pathogens.

Infectious Disease Society of America (IDSA)

The clinical and diagnostic recommendations from the IDSA's Diagnostics Committee (Hanson et al. 2024), provided comprehensive recommendations for the diagnosis of respiratory infections. These guidelines emphasize the importance of using nucleic acid amplification tests (NAATs) for accurate detection of pathogens in respiratory specimens. When used appropriately, multiplex molecular pneumonia syndromic panels can offer a more timely opportunity for optimizing treatment compared to traditional culture methods.

- For hospitalized patients, especially those in intensive care units, the guidelines suggest comprehensive respiratory panel testing to guide appropriate antimicrobial therapy.
- In outpatient settings, testing is recommended for patients with severe symptoms or those at high risk for complications, such as the elderly or immunocompromised individuals.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The FDA has approved a number of devices for use in Respiratory viral panel multiplex nucleic acid assay testing. Refer to the following website for more information (use product codes OCC, OEM, and QOF): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

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Policy History/Revision Information

Date	Summary of Changes
06/01/2025	• New Medical Policy

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

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