

LCD - Respiratory Pathogen Panel Testing (L39027)

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National Government Services, Inc.	MAC - Part B	06102 - MAC B	J - 06	Illinois
National Government Services, Inc.	MAC - Part B	06202 - MAC B	J - 06	Minnesota
National Government Services, Inc.	MAC - Part B	06302 - MAC B	J - 06	Wisconsin
National Government Services, Inc.	A and B and HHH MAC	13102 - MAC B	J - K	Connecticut
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LCD Information

Document Information

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LCD Title

Respiratory Pathogen Panel Testing

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Proposed LCD in Comment Period

N/A

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CMS National Coverage Policy

This LCD supplements but does not replace, modify or supersede existing Medicare applicable National Coverage Determinations (NCDs) or payment policy rules and regulations for respiratory pathogen panel testing. Federal statute and subsequent Medicare regulations regarding provision and payment for medical services are lengthy. They are not repeated in this LCD. Neither Medicare payment policy rules nor this LCD replace, modify or supersede applicable state statutes regarding medical practice or other health practice professions acts, definitions and/or scopes of practice. All providers who report services for Medicare payment must fully understand and follow all existing laws, regulations and rules for Medicare payment for respiratory pathogen panel testing and must properly submit only valid claims for them. Please review and understand them and apply the medical necessity provisions in the policy within the context of the manual rules. Relevant CMS manual instructions and policies may be found in the following Internet-Only Manuals (IOMs) published on the CMS Web site:

IOM Citations:

- CMS IOM Publication 100-02, *Medicare Benefit Policy Manual*,
 - Chapter 15, Section 80 Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests
- CMS IOM Publication 100-08, *Medicare Program Integrity Manual*,
 - Chapter 13, Section 13.5.4 Reasonable and Necessary Provision in an LCD

Social Security Act (Title XVIII) Standard References:

- Title XVIII of the Social Security Act, Section 1862(a)(1)(A) states that no Medicare payment shall be made for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury.
- Title XVIII of the Social Security Act, Section 1862(a)(7). This section excludes routine physical examinations.

Code of Federal Regulations (CFR) References:

- CFR, Title 42, Volume 2, Chapter IV, Part 410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions
- CFR, Title 42, Volume 2, Chapter IV, Part 411.15(a), Particular services excluded from coverage
- CFR, Title 42, Volume 2, Chapter IV, Part 493, Laboratory Requirements

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Compliance with the provisions in this policy may be monitored and addressed through post payment data analysis and subsequent medical review audits.

History/Background and/or General Information

Diagnostic testing for identification of pathogens that are causative for respiratory infections has evolved over the years. The aim is for rapid, accurate, and sensitive identification in an effort to improve patient outcomes through improved clinical decision making. These new technologies include nucleic acid-based amplification techniques. The focus of this LCD is respiratory pathogen panel testing, which typically includes detection for multiple virus pathogens by amplification of target DNA and is currently the most popular technique that can provide rapid, accurate, and sensitive results.¹

Even with the widespread use of respiratory pathogen panel testing, only a few methods are available that not only detect respiratory pathogens but are also U.S. Food and Drug Administration (FDA) approved. Please see the FDA link for approved/cleared respiratory pathogen panel tests. <https://www.fda.gov/>.² It is recognized that labs may not have FDA approval/clearance of their products, i.e. laboratory developed tests (LDTs). At the time of this publication, tests are not limited to FDA approved/cleared products only. Coverage for tests is based on demonstration of analytical and clinical validity and clinical utility at a level that meets the Medicare medically reasonable and necessary requirement.

Covered Indications

Respiratory pathogen panel testing in the outpatient by a Part B provider (e.g., physician's office, independent clinical laboratory) will be considered medically reasonable and necessary when all of the following are met:

1. Panels with ≤ 5 respiratory pathogens are performed, and **BOTH** of the following criteria are met:
 - The outpatient setting is equipped to deliver timely results **AND**,
 - For patients where the test result aids clinical management with the goal of an improved health outcome for the patient.

Limitations

The following is considered not medically reasonable and necessary:

1. Panels with >5 respiratory pathogens performed in the Part B outpatient setting.³

Notice: Services performed for any given diagnosis must meet all of the indications and limitations stated in this policy, the general requirements for medical necessity as stated in CMS payment policy manuals, any and all existing CMS national coverage determinations, and all Medicare payment rules.

Summary of Evidence

Introduction

This evidence review focuses on respiratory pathogen panel testing in the outpatient setting and whether the evidence is adequate to draw conclusions about improved health outcomes for the Medicare population. In general, improved health outcomes of interest include patient mortality and morbidity, as well as patient quality of life and function. The current clinical evidence is based on guideline recommendations and clinical studies that demonstrate the clinical utility of this testing. Specific outcomes of these trials in the outpatient setting are focused on accurate detection and identification of the pathogens in an effort to help guide clinical decision making. In other words, does performance of this test in the outpatient setting affect patient care, and ultimately, lead to reduced morbidity and mortality from respiratory infections in the Medicare population. Accurate, rapid test results have the potential to alter clinical management, such as initial medication prescription and safe medication de-escalation, which will result in improved patient health outcomes.

Internal Technology Assessment

PubMed® was searched for prospective clinical trials that included the terms molecular and respiratory. The studies that were found using these terms were then screened for applicability to the adult outpatient population. Only two studies were found that met the inclusion criteria. A search utilizing the terms molecular and pneumonia found no new studies. The terms panel and respiratory had 121 results and respiratory and immunocompromised had 59 results. The studies were then screened for inclusion of adults and outpatient settings. Guidelines were searched for respiratory infections, especially those which included patients who are immunocompromised. Additional studies were found upon review of the bibliographies within other search criteria. For inclusion in review, studies must be published in the English language and be specific to the human population. All countries of origin were included if broad inclusion for the clinical studies met the criteria. Ultimately, prospective studies that included adults, had identifiable outpatients, and had clinical utility outcomes for respiratory pathogen panel tests that primarily change the clinician decision making as the surrogate for patient outcomes of morbidity and mortality were included.

Systematic Review

Vos et al 2018³ systematically reviewed evidence on diagnostic accuracy and clinical utility for rapid (results < 3 hours) molecular diagnostics in comparison to conventional molecular tests for respiratory viruses. The review was conducted in a standardized, systematic manner and followed the guidance of the Cochrane DTA Working Group. Inclusion, exclusion, and statistical analysis plan are listed in the article and supplementary materials. In estimating diagnostic accuracy, 63 separate reports were included in the meta-analysis from 56 individual DTA publications. The median sample size in these reports was 95 patients. Reports evaluated 14 commercial molecular rapid diagnostic tests. Viruses evaluated include 29 studies of influenza A and B, 20 studies of influenza A, B, and RSV, and 14 studies of panels. Study populations included both children and adults, but ages were not reported. Results revealed the pooled sensitivity of all the tests was 90.9% (95% CI, 88.7% - 93.1%) and the pooled specificity was 96.1% (95% CI, 94.2% - 97.9%). For clinical impact evaluation, 15 studies met inclusion criteria. The authors note that

these studies had large variation in design and quality. Study design included 5 studies that were randomized diagnostic impact trials, 6 studies using a nonrandomized before-after design, and 4 observational non-comparative studies. Seven studies were manufacturer sponsored. Most studies included only adult patients. The Film Array test was the most frequent diagnostic intervention. Clinical outcomes are listed and categorized in Table 4 of the article. Results show implementation of rapid molecular tests did not decrease the number of antibiotic prescriptions or duration of antibiotic treatment. The number of hospital admissions was not reduced by rapid molecular testing. Safety outcomes did not differ between the intervention and control groups. There was an increased appropriate use of oseltamivir in influenza positive patients. The authors concluded: "In conclusion, rapid molecular tests for viral pathogen detection provide accurate results. Even though results on clinical impact of rapid diagnostic tests are conflicting, there is high-quality evidence that rapid testing might decrease the length of hospital stay and might increase appropriate use of oseltamivir in influenza virus-positive patients, without leading to adverse results. We therefore suggest considering implementation of rapid molecular tests within hospital settings and recommend performance of high-quality randomized studies."³

Additional Clinical Trials

Brittain-Long 2011⁴ designed a randomized study to determine if multiplex testing for respiratory pathogen identification in adult patients with symptoms of acute respiratory infections would have an impact on antibiotic prescription rate in primary care settings. The patients had to have a diagnosis of an acute respiratory infection, defined as a history of at least two of the following symptoms: coryza/nasal congestion/sneezing, sore throat/odynophagia, cough, pleuritic chest pain, shortness of breath or fever for which the physician found no other explanation, with a duration of less than 14 days. The sample size included 447 patients, though 406 were available for analysis. Nasopharyngeal and throat swabs were collected and a multiplex PCR test with 13 viruses and 2 bacteria was performed, at 12 outpatient sites in Sweden. Samples were collected at the initial visit and at the follow-up visit 10 days later. Patients were randomized to one of two cohorts. In the rapid cohort, clinicians received the results on the day following patient inclusion into the study (within 24 hours for the majority of patients), or the delayed cohort, where clinicians received the results eight to twelve days later. The primary outcome was antibiotic prescription rate at the initial visit and the secondary outcome was the total antibiotic prescription rate during the study period. Patient management was treating physician discretion. For the rapid result, 5.4% (9 of 202) patients received antibiotics at the initial visit compared to 12.3% (25 of 204) (P = 0.0005) of patients in the delayed result group. Upon stratification by symptom duration ≤ 5 days, patients in the rapid result group received fewer antibiotic prescriptions than patients in the delayed result group. At follow-up there was no difference between the groups: 13.9% (28 of 202) in the rapid result group and 17.1% (35 of 204) in the delayed results group received antibiotics. The authors conclude, "In conclusion we have shown that access to a multiplex RT-PCR assay for the aetiologic diagnosis of ARTIs may reduce the prescription rate of antibiotics at the initial visit in an outpatient setting. To sustain the effect, it seems necessary to define how to follow and manage the patient according to the result of the test, which warrants further investigation."⁴

Echavarría et al 2018⁵ aimed to determine if timely diagnosis of respiratory infection etiology could have an impact on medical management in the emergency department, in Buenos Aires, Argentina. The study design was a randomized, non-blinded study in children and adults with signs/symptoms of acute respiratory infection with onset within the preceding 7 days that compared two methods of testing. Patients were randomized to either the Film Array respiratory panel or immunofluorescence assay (IFA) over two seasons. Median time from sample collecting to reporting was under two hours for the FilmArray-RP and 26 hours by IFA. A total of 156 children and 276 adults were included. Changes in medical management included any change between the initial intention to treat with antibiotics or oseltamivir and/or to order complementary studies and the final decision, after test results were available. Results were reported by telephone to the physician who initially saw the patient, and at that moment the study team questioned the physician about any changes in medical management between the original plan previously documented on the standardized form and the final management plan that included the test results. Changes in medical management were observed in both groups, however patients in the FilmArray respiratory panel group were associated with changes in medical management with an odds ratio of 15.52, 95% CI; 1.99 – 120.83, in adults. This study was partially funded by a stakeholder grant.

May et al 2019⁶ is a randomized clinical trial designed to evaluate the impact of a multiplex respiratory test versus usual care control in an emergency department. Pediatric and adult patients were included, and 191 patients were enrolled (61 patients age 18 or older in the intervention arm and 59 age 18 or older in the control arm) that met upper respiratory infection or influenza-like illness inclusion criteria. Average age of the adult patients is not listed, but comorbidities are listed. The primary outcome was an antibiotic prescription, with the secondary outcomes as antiviral prescription, emergency department disposition, and length of hospital stay. Clinicians and patients were not blinded. The goal of test result reporting to the clinicians was within 2 hours. Power calculations were done; however, enrollment did not reach goal due to budgetary constraints. Some patients in the intervention arm received antibiotics despite having a virus detected. "The magnitude of antibiotic reduction was greater in children (-19%) vs adults (-9%, post hoc analysis). There was no difference in antiviral use, length of stay or disposition." The authors concluded, "Further evaluation of rapid multiplex testing in the ED could see changes in outcomes if the limitations of this study were addressed. This mainly includes identifying the right patient population where testing can alter patient care (vs targeted testing or no testing) and focusing on implementing comprehensive stewardship strategies alongside diagnostic tools to ensure that testing is utilized appropriately and effectively."⁶

Guidelines

The American Thoracic Society (ATS) and Infectious Diseases Society of America's (IDSA) clinical practice guideline⁷ addresses high priority questions using systematic reviews of high-quality studies. It is noted that the evidence base was often insufficient and emphasizes the continued importance of clinical judgment and experience, and the great need for research. "Community-acquired Pneumonia (CAP) is an extraordinarily heterogeneous illness, both in the range of responsible pathogens and the host response." The need for individualized patient management is stressed. The guideline focuses on patients in the U.S. who have not recently completed foreign travel and do not have an immunocompromising condition, such as inherited or acquired immune deficiency or drug-induced neutropenia, including patients actively receiving cancer chemotherapy, patients infected with HIV with suppressed CD4 counts, and solid organ or bone marrow transplant recipients. In the conclusion it is stated: "Unfortunately, microbiological testing has yet to deliver fast, accurate, and affordable testing that result in proven benefit for patients with CAP in terms of more rapid delivery of targeted therapy or safe de-escalation of unnecessary therapy. Exceptions include rapid testing for MRSA and influenza. Until we have such widely available (and affordable) tests, therapy for many or most patients with CAP will remain empiric. Therefore, clinicians need to be aware of the spectrum of local pathogens, especially if they care for patients at a center where infection with antibiotic-resistant pathogens such as MRSA and *P. aeruginosa* are more common."⁷

The CHEST Guideline and Expert Panel Report⁸ is a 2019 systematic review that developed recommendations related to acute cough due to suspected pneumonia or influenza. Literature search did not identify an article addressing the question of whether microbiological testing in addition to clinical judgment rather than clinical judgment alone should be used to confirm pneumonia in outpatients with acute cough. The below suggestion is offered:

"For outpatient adults with acute cough and suspected pneumonia, we suggest that there is no need for routine microbiological testing (Ungraded Consensus-based statement)

Remarks: Microbiologic testing should be considered if the results may result in a change of therapy."⁸

The IDSA's 2018 evidence-based clinical practice guideline for seasonal influenza⁹ notes that timely diagnosis of influenza may increase the appropriate use of antivirals and decrease the inappropriate use of antibiotics. The grading of evidence is based on the U.S. Public Health Service Grading System for ranking recommendations in clinical guidelines. The recommendations for outpatient testing and panel testing include the following statements:

- "Clinicians should use rapid molecular assays (i.e., nucleic acid amplification tests) over rapid influenza diagnostic tests (RIDTs) in outpatients to improve detection of influenza virus infection (A-II)."
- "Clinicians should use multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza

viruses, in hospitalized immunocompromised patients (A-III).”

- “Clinicians can consider using multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized patients who are not immunocompromised if it might influence care (e.g., aid in cohorting decisions, reduce testing, or decrease antibiotic use) (B-III).”⁹

Consensus Statements

Ramirez et al's 2020 Treatment of Community-Acquired Pneumonia in Immunocompromised Adults¹⁰ is a consensus document addressing initial treatment of the immunocompromised patient who presents to the hospital with community acquired pneumonia. It is noted that the number of immunocompromised people at risk for CAP is increasing and is estimated to be 3% of the U.S. population. The document includes a table (Table 2)¹⁰ that identifies patient conditions qualifying patients as immunocompromised, which is listed below.

- Primary immune deficiency diseases
- Active malignancy or malignancy within 1 yr of CAP, excluding patients with localized skin cancers or early-stage cancers (e.g., stage 1 lung cancer)
- Receiving cancer chemotherapy
- HIV infection with a CD4 T-lymphocyte count <200 cells/ μ L or percentage, 14%
- Solid organ transplant
- Hematopoietic stem cell transplantation
- Receiving corticosteroid therapy with a dose \geq 20mg prednisone or equivalent daily for \geq 14d or a cumulative dose >700mg of prednisone
- Receiving biological immune modulators
- Receiving disease-modifying antirheumatic drug or other immunosuppressive drugs (e.g., cyclosporin, cyclophosphamide, hydroxychloroquine, methotrexate)

They note patients with common comorbid conditions such as diabetes, chronic lung disease, liver disease, kidney disease and the elderly and frail are relatively immunocompromised; however, these patients are typically infected with the same spectrum of organisms that cause CAP in younger or healthier adults, with their treatments covered in the current guidelines. For the immunocompromised, as defined in this article, they recommend a low threshold for hospitalization, with the suggestion of a comprehensive microbiological workup with the goal to perform pathogen-directed therapy and de-escalation of therapy. The microbiologic workup should be individualized and includes a table with specific immune deficiencies and associated respiratory pathogens. Additionally, a negative nasopharyngeal PCR result does not rule out a viral pneumonia, and with high suspicion the PCR should be done on bronchoscopy samples. Furthermore, finding a virus by PCR does not rule out a bacterial infection. The document does not address outpatient microbiological studies.

Contractor Advisory Committee (CAC) Advisory Panel Meeting

General consensus from the Novitas Solutions and First Coast Service Options CAC panel is that there is accuracy and reliability in these respiratory pathogen panels and that the results of this testing may improve patient health outcomes. The CAC panel also noted that there is a gap in the literature when it comes to patient health outcomes related to the results and how it affects patient treatment and/or management especially with pathogens of lower prevalence that some of the respiratory pathogen panels include.

Analysis of Evidence (Rationale for Determination)

Most respiratory infections are self-limited in immunocompetent hosts, with some exceptions. For more serious infections such as CAP, patients can present with a variety of symptoms, and it can be difficult to make the correct diagnosis and enact appropriate treatment such as medication or hospitalization. Clinicians use information obtained from a detailed patient history and physical, and then may require additional information such as chest x-ray and

complete blood count with differential to help in decision making. A particular concern is identifying pathogens that have targeted therapies. Clinician decision making for patient management includes a compilation of an array of information. In order to avoid the consequences of a potential serious untreated infection, empirical treatment with antibiotics is common even though viruses are in many instances the causative agents.

In an attempt to provide appropriate targeted therapies, a diagnostic work-up could include tests aimed at pathogen identification. Respiratory pathogen panel testing has the advantage of rapid detection of multiple organisms, which in theory would improve patient care via improved clinician decision-making. However, limitations exist in understanding ideal testing strategies and test interpretation.¹¹ Sensitivity and specificity appear to be established in respiratory pathogen panel testing, though there may be important differences within panels for individual pathogens.^{1,12,13,14,15,16,17,18} Infection occurrence by a particular pathogen varies by region and time, in addition to patient specific risk factors.¹⁹ Predictive value is the tool that would better help the clinician narrow pathogen identification and select the appropriate course of management.²⁰ Pathogen prevalence as a causative organism varies as noted and prevalence is related to predictive value; the test panels are static and may not include the organism causing the infection. Additionally, it remains unclear how to interpret a panel with multiple positive results; for instance, co-infection, which does occur with varying frequency, versus contaminant, versus false positives.¹⁹ These limitations may serve to lessen clinician confidence in panel results and decrease the value of these panels as a decision-making tool.

Data of good quality for the clinical utility of multiplex respiratory pathogen testing is limited.²¹ The strongest evidence comes from Vos 2017³, a systematic review and meta-analysis that examined clinical impact. The 15 studies examining clinical utility met broad inclusion criteria, and included various study designs, pediatric and adult patients, outpatient and inpatient settings, and different healthcare systems. The authors concluded that rapid molecular tests for viral pathogen detection provide accurate results, but that results on clinical impact were conflicting. They do suggest consideration of rapid molecular tests within hospital settings. Brittain-Long 2011⁴ is a study in the Swedish healthcare system that did not show a total reduction in appropriate outpatient antibiotic therapy with panel testing. Echavarría 2018⁵ aimed to compare timely patient management by comparing two diagnostic tests. It is a study in a different healthcare system as is Brittain-Long;⁴ the generalizability to the U.S. healthcare system is unclear. The May⁶ study was limited in small sample size making it difficult to draw conclusions. Summarizing the clinical evidence: in the outpatient immunocompetent population, results from respiratory pathogen identification via the current panels appears to be insufficient to assist in clinical decision making to improve health outcomes, with the exception of testing to identify influenza.^{3,22} Additionally, it is recognized that it is important to identify COVID-19 as a cause of infection.

Clinical practice guidelines are helpful in assisting clinicians in patient management. The CAP guideline by ATS and IDSA⁷ recommends empiric treatment, stressing the need for clinicians to be aware of the current pathogens in their locality and to treat appropriately. They note rapid testing for MRSA and influenza as being helpful in decision making, but that other microbiological testing has yet to result in proven benefit as far as rapid targeted therapy, or safe de-escalation of apparent unnecessary therapy. The CHEST guideline⁸ and expert panel report for acute cough due to suspected pneumonia or influenza suggests that there is no need for routine microbiological testing and that it could be considered if the results may result in a change of therapy. The IDSA guideline⁹ on management of seasonal influenza recommends multiplex testing in hospitalized immunocompromised patients and in those hospitalized but not immunocompromised if it might influence care. There is no current support in guidelines for outpatient multiplex testing for respiratory pathogens.

In the immunocompromised, where concerns are great for poor outcomes, the data comes primarily from the inpatient setting. In the inpatient setting, results are inconsistent.^{23,24} To further help clinical decision-making, Ramirez 2020¹⁰ addresses initial treatment of the immunocompromised, as defined in the document, and recommends a low threshold for hospitalization, with the suggestion of a comprehensive individualized microbiological work-up. The document does not address outpatient microbiological studies.

The CAC advisory panel meeting discussion reflected current literature. They noted accuracy and reliability in these

multiplex panels and that the results of this testing may improve patient health outcomes, however there is a gap in the literature when it comes to patient health outcomes related to the results and how it affects patient treatment and/or management.

In contrast, there is evidence to support influenza testing in appropriate patients, particularly in the hospital inpatient setting.^{9,25} The importance of differentiating COVID-19 from influenza, cannot be understated, which is reflected in the CDC²⁶ development of a 3 –pathogen respiratory pathogen panel assay to differentiate COVID-19 from influenza A and B.

The implementation of rapid molecular diagnostics to directly affect patient outcomes and tackle antibiotic resistance requires a thoughtful approach. Timely reporting, clinician education, decision support and evidence-based guidelines based on test results are some of the processes that may improve patient outcomes and lessen antibiotic resistance.^{3,20,27} Antibiotic resistance is a critical concern and parallels appropriate patient management.

New diagnostic tools aimed at rapid and accurate pathogen identification hold great promise for patient management, and meaningfully address the critical issue of antibiotic resistance. In consideration of improving patient outcomes, high-quality research is critically needed to fulfill this promise.

In summary, the studies demonstrate that other than testing for influenza and recognition of the importance of identifying COVID-19, testing for multiple pathogens using respiratory pathogen panel tests have not been proven to impact clinical decision making resulting in improved patient outcomes. Therefore, respiratory pathogen panel tests for greater than 5 respiratory pathogens are not medically reasonable and necessary for the purposes of Medicare coverage.

General Information

Associated Information

Please refer to the related Billing and Coding Article: Respiratory Pathogen Panel Testing (A58741) for documentation requirements, utilization parameters and all coding information as applicable.

Sources of Information

N/A

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Revision History Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

[A58741 - Billing and Coding: Respiratory Pathogen Panel Testing](#)

[A58890 - Response to Comments: Respiratory Pathogen Panel Testing](#)

Related National Coverage Documents

N/A

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