Molecular Respiratory Infection Pathogen Panel (RIPP) Testing

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Introduction

Molecular respiratory infection testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure(s) addressed by this guideline</th>
<th>Procedure code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioFire FilmArray Respiratory Panel (RP) EZ</td>
<td>0098U</td>
</tr>
<tr>
<td>BioFire FilmArray Respiratory Panel (RP)</td>
<td>0099U</td>
</tr>
<tr>
<td>BioFire FilmArray Respiratory Panel 2 (RP2)</td>
<td>0100U</td>
</tr>
<tr>
<td>BioFire FilmArray Pneumonia Panel</td>
<td>0151U</td>
</tr>
<tr>
<td>ePlex Respiratory Pathogen (RP) Panel</td>
<td>0115U</td>
</tr>
<tr>
<td>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 or subtypes, 3-5 targets</td>
<td>87631</td>
</tr>
<tr>
<td>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 or subtypes, 6-11 targets</td>
<td>87632</td>
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</tbody>
</table>
What is Respiratory Pathogens Panel Testing

Definition

Respiratory pathogens panel testing is the use of molecular technologies to detect respiratory pathogens directly in a clinical sample.

- In spite of the continued utilization of conventional diagnostic methods in clinical microbiology laboratories, the expanded availability of molecular methods for detection of pathogens directly in clinical specimens is changing the paradigm for diagnosis and management of patients with infectious diseases. One of the recent reasons for these changes has been the development of syndromic-based multiplex molecular panels, in this case, for respiratory presentations, with the ability to simultaneously detect, differentiate, and even subtype viral/bacterial pathogens in patient specimens.

- Viral pathogens are the most common cause of respiratory tract infections. Seasonal influenza contributes to substantial morbidity and mortality each year in the United States. However, in a large portion of patients with respiratory tract infections, other viruses and non-cultivable organisms have been found to cause substantial morbidity and mortality.

- The ability to detect a large number pathogens rapidly and with high sensitivity and specificity has the potential to transform clinical microbiology as a continuing critical component of laboratory medicine. However, it is important to consider whether these tests should be front-line tests used for all patients with acute respiratory illness or whether their use should be limited to specific patients.
Test Information

Introduction

This section of the guideline contains information about testing for respiratory pathogens.

- Respiratory panels may provide sample-to-answer results, using integrated nucleic acid extraction, amplification and detection with testing times of as little as 1 hour, typically using nasopharyngeal swab specimens. Several test systems have received FDA-clearance for the detection of respiratory tract pathogens, which has facilitated their rapid integration into routine testing. Other test platforms may include laboratory-validated panels that are customized for clinicians at their service clinical practice networks.

- The menu of analytes on several panels is for the first time providing access to routine testing for pathogens that have previously been difficult to detect, or for which testing was only available at reference laboratories (i.e. norovirus, coronaviruses, Chlamydophila pneumoniae, Mycoplasma pneumoniae). These assays detect 12-20 pathogens and some include pathogens that typically cause different manifestations of infection, although they infect the same organ system.

- Analytically, the molecular assays usually exhibit comparative or superior detection rates compared to conventional methods which also result in an increased rate of diagnosis for affected patients. In addition, multiplex polymerase chain reaction (mPCR) molecular panels allow laboratories to consolidate testing for a broad range of pathogens from the same samples. This consolidation provides opportunities to eliminate conventional testing methodologies, including direct fluorescent antibody (DFA) and cell culture for the detection of respiratory viruses.

- However, the fixed nature of the mPCR panels raises the concern that they might include pathogens causing infections with sufficiently clinical/epidemiological diversity, such that, in turn, simultaneous testing for those pathogens should be rare. Alternatively, the differences might be detectable by rapid, accurate and inexpensive tests (e.g. the Gram stain) that are part of routine testing. It is reasonable to assert that negative test results for common pathogens should typically precede testing for uncommon pathogens.

Guidelines and Evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to respiratory pathogens panel testing.
American Society of Transplantation/Canadian Society of Transplantation

Manuel (2013) was modified from a previous guideline published in the American Journal of Transplantation in 2009; 9(Suppl 4): S166–S172, and endorsed by American Society of Transplantation/Canadian Society of Transplantation. Guidelines were again updated in 2019 by the American Society of Transplantation Infectious Diseases Community of Practice:

• “Since one cannot clinically distinguish disease caused by any of the respiratory viruses, diagnosis using broad ranging techniques should be considered particularly in the early period after transplantation or augmented immunosuppression and during respiratory viral season, particularly among lung transplant recipients.”

• “Nucleic acid amplification assay appear to be the most sensitive…and allow for simultaneous detection of a broad range of respiratory pathogens from a single sample and are therefore the preferred diagnostic testing method for immunocompromised patients. Multiplex PCR assays provide the advantage of identification of viruses not routinely found by conventional methods…”

Infectious Disease Society of America (IDSA)

In the 2018 IDSA practice guidelines for the “Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza,” recommendations for diagnostic testing include:

• “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 (eg, aid in cohorting decisions, reduce testing, or decrease antibiotic use) (B-III).”

British Committee for Standards in Hematology

A joint working group established by the Hemato-oncology subgroup of the British Committee for Standards in Hematology, the British Society for Bone Marrow Transplantation and the UK Clinical Virology Network has reviewed the available literature and made recommendations in 2016 for the diagnosis and management of respiratory viral infections in patients with hematological malignancies or those undergoing hematopoietic stem cell transplantation. To illustrate:

• “It is currently recommended that the diagnosis of respiratory viral infections is made by quantitative nucleic acid amplification tests (NAATs), generically referred to hereafter as PCR; clinicians should be able to liaise with their virology laboratory colleagues regarding the interpretation of PCR results … A panel of viruses should be included for PCR testing, including parainfluenza type 4.”
German Society for Haematology and Medical Oncology

A panel of 18 clinicians from the Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology convened to assess the available literature and provide 2016 recommendations on the management of community acquired respiratory virus infections including influenza, respiratory syncytial virus (RSV), parainfluenza virus (PIV), human metapneumovirus (hMPV) and adenovirus. Two relevant excerpts include:9

• “Most data on this topic originate from patients following allogeneic stem cell transplantation (allo-SCT), and we know little about community-acquired respiratory virus (CARV) infections in cancer patients outside the setting of allo-SCT. However, in recent years increasing evidence has been gathered about other cancer patients, revealing clinical relevance of CARV infections in non-transplant patients. Therefore, this guideline discusses CARV infections in all cancer patients with ongoing relevant immunosuppression. It is left to the treating physician to assess the degree and relevance of immunosuppression in the individual patient.”

• “In the era of multiplex-test kits, it is difficult to make a definite recommendation with regard to which viruses should be looked for. In the absence of any reliable data regarding this question, the panel feels that it is wise to search for influenza, RSV, PIV and viruses currently prevalent in the local environment in all immunosuppressed cancer patients presenting with symptoms. Patients with more severe disease (for example pneumonia or critical illness) may have the panel broadened to include hMPV and adenovirus and even viruses that only rarely cause lower respiratory tract infections like rhinovirus and coronavirus. However, evidence for this approach is low and it is strongly advisable to define local guidelines on this topic.”

Fourth European Conference on Infections in Leukemia

A working group of the Fourth European Conference on Infections in Leukemia (ECIL-4) 2011 reviewed the literature on community-acquired respiratory virus (CARV), graded the available quality of evidence, and made the relevant diagnostic recommendations according to the Infectious Diseases Society of America (IDSA) grading system:10

• First-line diagnostic testing should be performed for influenza A and B, RSV, and human parainfluenza viruses (HPIV) (IDSA Grade A II).

• Testing for other CARVs should be considered according to risk of exposure and the local epidemiology, or if testing for the firstline CARVs is negative (IDSA Grade B III).

Expert Written and Peer Reviewed Articles

There have been additionally referenced indications for the use of (typically viral) respiratory pathogen panels, such as for adult patients appearing acutely ill, who are potential hospital admissions, where, for example, such panel testing would be ordered
in the emergency department (ED). To illustrate, two randomized controlled studies have described some possible favorable outcomes in the ED:

- **Brendish (2017)**\(^{11}\) where respiratory viral panel testing did not ... “reduce the proportion of patients treated with antibiotics. However, the primary outcome measure failed to capture differences in antibiotic use because many patients were started on antibiotics before the results of point-of-care testing (POCT) could be made available. Although POCT was not associated with a reduction in the duration of antibiotics overall, more patients in the POCT group received single doses or brief courses of antibiotics than did patients in the control group. POCT was also associated with a reduced length of stay and improved influenza detection and antiviral use, and appeared to be safe.”

- **Brittain-Long (2011)**\(^{2}\) found that ... “In the group of patients randomised for a rapid result, 4.5% (9 of 202) of patients received antibiotics at the initial visit, compared to 12.3% (25 of 204) (P = 0.005) of patients in the delayed result group. At follow-up, there was no significant difference between the groups: 13.9% (28 of 202) in the rapid result group and 17.2% (35 of 204) in the delayed result group (P = 0.359), respectively.” ... with the conclusion that ...“Access to a rapid method for etiologic diagnosis of acute respiratory tract infections (ARTIs) may reduce antibiotic prescription rates at the initial visit in an outpatient setting. To sustain this effect, however, it seems necessary to better define how to follow and manage the patient according to the result of the test, which warrants further investigation.”

Furthermore, critically-ill adult patients, particularly intensive care unit (ICU) patients, lack the same evidentiary level for metrics such as the reduction of unnecessary antibiotic use, which is a major cause of morbidity in hospitalized patients. However, case series studies make a convincing case that respiratory viral pathogens are of considerable relevance in the ICU setting. To illustrate, Choi (2017)\(^ {10}\) found that viral infection is common in adult patients with severe pneumonia. About one-third of patients with severe community-acquired pneumonia or healthcare-associated pneumonia had viral infections, and the mortality from viral infection and bacterial infection was comparable. The viral agents involved in descending order of prevalence were rhinovirus, parainfluenza virus (Types 3, 1, 2, and 4, respectively), hMPV, influenza, RSV, and, more infrequently, cytomegalovirus, human coronavirus, adenovirus, and enterovirus. Furthermore, Voiriot (2016)\(^ {12}\) observed a relatively more complicated course among ICU patients with mixed bacterial and viral respiratory infections.

Outcome data for use of multiplex panels in adult ambulatory patients is generally more mixed. For example, Green et al. (2016) showed that use of a multiplex panel (Biofire FilmArray v1.7 respiratory panel) in outpatient adults (VA patients) led to increased rates of oseltamivir and decreased rates of antibiotics for patients diagnoses with influenza, but there was no significant difference in antibiotic prescription rates between patients who tested negative and those who had a non-influenza virus—suggesting a targeted influenza diagnostic may have been adequate in their population.\(^ {14}\) When specifically evaluating patients at an ambulatory cancer center, however, Krantz et al. (2019) found that multiplex viral testing on day 0 decreased the
risk of antibiotic prescriptions by half compared to patients who were not tested on day 0.\textsuperscript{15}

It should be noted that the utility of multiplex testing for each institution and patient population should be interpreted in the context of the turn-around-time (TAT) of the assay(s) available. Wabe et al (2019) evaluated outcomes of patients presenting to the emergency department before and after a transition from a standard multiplex PCR performed at a centralized laboratory (TAT of 26.7 hours; 16 viruses) to a rapid hospital-based assay that only detects influenza A, influenza B, and RSV (TAT 2.4 hours).\textsuperscript{16} A small, but statistically significant, decrease in hospital admissions was noted after implementing the more limited, but rapid assay.

Finally, however, there were no substantive peer-reviewed full articles which addressed the relative clinical impact of ordering respiratory pathogen panels, with differing numbers of infectious targets.

**Criteria**

**Introduction**

Requests for molecular respiratory infection pathogen panel (RIPP) testing are reviewed using the following clinical criteria.

The presence of acute respiratory symptoms in members 17 years of age or younger, OR

The presence of acute respiratory symptoms in members of any age who are:

- Immunocompromised (as defined by ICD-10 codes), OR
- Immunocompetent and receiving care for their acute respiratory symptoms in a hospital setting as evidenced by the following
  - Place of service code on the claim is: 19, 22, or 23 , or
  - Bill type code on the claim is: 13X or 14X, OR

The following is a contraindication to RIPP testing in members 18 years of age or older:

- Presence of respiratory symptoms that suggest a specific respiratory pathogen in an immunocompetent adult.

Molecular RIPP testing is limited to the minimum number of targets needed for therapeutic decision making. When ordering any configuration of infectious disease targets, whether using RIPP or conventional testing, the medical record should clearly indicate the differential diagnosis of possible microorganisms based upon member history and presenting signs/symptoms.

It is not necessary to repeat a respiratory pathogen panel to ensure a causative organism is cleared. If test of cure is indicated for a particular organism, individual
organism testing should be used. Therefore, repeat testing of any panel within a two week time frame will not be reimbursed.

Billing and reimbursement

- No more than one respiratory virus panel should be necessary on a single date of service. Therefore, only one unit of the same panel code will be reimbursable and two different panel codes (87631, 87632, 87633, 0098U, 0099U, 0100U, 0115U, or 0151U) cannot be billed on the same date of service.
- More than one type of test for the same organism will not be reimbursable for the same date of service (e.g., 87631 and 87634 may not be billed together).
- A code representing only the minimum panel necessary to detect the necessary targets should be billed. If the laboratory’s testing platform consists solely of a panel of multiple targets, yet only a subset of the organisms are considered medically necessary based on the above criteria, the lab may request reimbursement for that subset of organisms using a procedure code that does not represent all organisms included on the panel (e.g., bill 87632 if only 8 targets are necessary even if 12 or more targets were tested as part of a panel usually billed with 87633 or 0151U).

Note  Inpatient services are beyond the scope and domain of this guideline.

Although outbreak investigations may sometimes require use of RIPP testing, the public health evaluations of such outbreaks are beyond the scope and domain of this guideline.

ICD10 codes

ICD10 codes in this section may be used to support medical necessity as described in the above criteria.

**ICD10 Codes Indicating Cancer, Transplant, or Other Immunocompromise**

<table>
<thead>
<tr>
<th>ICD10 Code or Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B20</td>
<td>Human immunodeficiency virus [HIV] disease</td>
</tr>
<tr>
<td>B59</td>
<td>Pneumocystosis</td>
</tr>
<tr>
<td>C00.X-C96.X</td>
<td>Malignant neoplasms</td>
</tr>
<tr>
<td>D37.X-D48.X</td>
<td>Neoplasms of uncertain behavior, polycythemia vera and myelodysplastic syndromes</td>
</tr>
<tr>
<td>D60.X-D64.X</td>
<td>Aplastic and other anemias and other bone marrow failure syndromes</td>
</tr>
<tr>
<td>D70.X-D77</td>
<td>Other disorders of blood and blood-forming organs</td>
</tr>
<tr>
<td>ICD10 Code or Range</td>
<td>Description</td>
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<td>---------------------</td>
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</tr>
<tr>
<td>D80.X-D89.X</td>
<td>Certain disorders involving the immune mechanism</td>
</tr>
<tr>
<td>E40-E46</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>I12.0</td>
<td>Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease</td>
</tr>
<tr>
<td>I13.11</td>
<td>Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease</td>
</tr>
<tr>
<td>I13.2</td>
<td>Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease</td>
</tr>
<tr>
<td>K91.2</td>
<td>Postsurgical malabsorption, not elsewhere classified</td>
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<tr>
<td>M35.9</td>
<td>Systemic involvement of connective tissue, unspecified</td>
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<tr>
<td>N18.5</td>
<td>Chronic kidney disease, stage 5</td>
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<tr>
<td>N18.6</td>
<td>End stage renal disease</td>
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<tr>
<td>T86.X</td>
<td>Complications of transplanted organs and tissue</td>
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<tr>
<td>Z48.2X</td>
<td>Encounter for aftercare following organ transplant</td>
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<tr>
<td>Z49.X</td>
<td>Encounter for care involving renal dialysis</td>
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<tr>
<td>Z94.X</td>
<td>Transplanted organ and tissue status</td>
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<tr>
<td>Z99.2</td>
<td>Dependence on renal dialysis</td>
</tr>
</tbody>
</table>

References

Introduction

The following references are cited in the guideline.


