

LCD - MoIDX: Molecular Syndromic Panels for Infectious Disease Pathogen Identification Testing (L39044)

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CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	05101 - MAC A	J - 05	Iowa
Wisconsin Physicians Service Insurance Corporation	MAC - Part B	05102 - MAC B	J - 05	Iowa
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	05201 - MAC A	J - 05	Kansas
Wisconsin Physicians Service Insurance Corporation	MAC - Part B	05202 - MAC B	J - 05	Kansas
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	05301 - MAC A	J - 05	Missouri - Entire State
Wisconsin Physicians Service Insurance Corporation	MAC - Part B	05302 - MAC B	J - 05	Missouri - Entire State
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Wisconsin Physicians Service Insurance Corporation	MAC - Part A	08101 - MAC A	J - 08	Indiana
Wisconsin Physicians Service Insurance Corporation	MAC - Part B	08102 - MAC B	J - 08	Indiana
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	08201 - MAC A	J - 08	Michigan
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LCD Information

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MOLDX: MOLECULAR SYNDROMIC PANELS FOR INFECTIOUS DISEASE PATHOGEN Identification Testing

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Issue

Issue Description

No changes in coverage. Under Bibliography 3. the broken link was removed.

Issue - Explanation of Change Between Proposed LCD and Final LCD

Title of policy changed, and other minor changes were made for clarification.

CMS National Coverage Policy

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Title XVIII of the Social Security Act, §1862(a)(1)(A) allows coverage and payment for only those services that are considered to be reasonable and necessary

42 CFR §410.32(a) Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions

CMS Internet-Only Manual, Pub. 100-02, Medicare Policy Manual, Chapter 15, §80 Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests, §80.1.1 Certification Changes

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This policy provides limited coverage for outpatient testing with panels using molecular syndromic panels for infectious disease pathogen identification testing. This policy does NOT address coverage for the inpatient setting.

This policy defines a panel as a test that detects > 1 pathogen. This policy also differentiates (where appropriate) between small, targeted panels (up to 5 pathogens) and larger, expanded panels (≥6 pathogens). This distinction is *primarily* applied to the Respiratory and Gastrointestinal Panels. A 'syndromic panel' is further defined as one that simultaneously detects multiple different pathogens associated with similar and overlapping clinical symptomatology.

This is NOT a coverage policy for metagenomic next-generation sequencing, mass spectrometry, or fluorescence in situ hybridization (FISH).

General Criteria For Coverage For A Molecular Syndromic Infectious Disease Pathogen Identification Panel Test

This Medicare Contractor will cover molecular syndromic infectious disease pathogen identification panel tests when ALL of the following criteria are met:

- The patient has a clinical indication for infectious disease testing:
 - For immunocompetent patients, the clinical indication includes a presumption of active infection OR infection-associated complications (which may include exacerbation of underlying disease) *that require the identification of a causative organism for appropriate management*. Atypical clinical presentations of disease are considered appropriate indications for special populations who may not present with classic symptoms of infection (i.e., the elderly).
 - For immunocompromised patients (i.e., those with weakened immune systems including those with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), patients who are taking immunosuppressive medications (i.e., chemotherapy, biologics, transplant-related immunosuppressive drugs, high-dose systemic corticosteroids) and those with inherited diseases that affect the immune system (i.e., congenital immunoglobulin deficiencies), atypical clinical presentations of disease are considered appropriate indications for testing. In this patient population, testing may be performed ONCE as part of a pre-transplant evaluation, regardless of the presence of symptoms.
 - **Note:** For certain panels, such as the Urogenital/Anogenital Panel, epidemiologic indication or potential exposure to pathogens as a result of a high-risk experience is considered a covered clinical indication, even in the absence of clinical symptoms. These are specifically noted below in **LIMITED COVERAGE FOR EXPANDED (>5 Pathogens) PANEL TESTING**.
- The results of testing will impact clinical management in a manner already demonstrated in the peer-reviewed published literature to improve patient outcomes.
- Testing is performed according to the intended use of the test in the intended patient population for which the

test was developed and validated.

- This includes performing the test using the intended sample types along with parallel testing that must accompany the test (i.e., the meningoencephalitis and bloodstream pathogen tests include requirements for parallel testing using conventional Gram stain and culture-based detection for correlation of results).
- This also includes the provision - by the laboratory to ordering providers - of the major limitations of a given panel test.
- An evaluation for more than 1 pathogen by molecular testing is necessary for patient management (testing for a single pathogen is NOT reasonable and necessary for the specific infection, patient, or indication). The panel performed includes *at least* the minimum pathogens required for clinical decision making for its intended use that can be reasonably detected by the test.
- Expanded panel testing is only indicated when targeted panel testing is not appropriate (i.e., will not provide sufficient information for the appropriate clinical management of the patient). See **LIMITED COVERAGE FOR EXPANDED (>5 Pathogens) PANEL TESTING** below.
- Services that do not have Food and Drug Administration (FDA)-cleared/approved indicated uses, as well as FDA-approved tests performed in ways not consistent with their intended-use labeling directions, will require registration with Molecular Diagnostic Services Program (MolDX®) and a Technical Assessment (TA) to demonstrate compliance of the service with this policy. Similarly, tests (and CPT codes) for which there are no accompanying ICD-10 codes in the associated Billing and Coding Article will require registration with MolDX® and a TA to demonstrate compliance of the service with this policy.
- Registered tests must demonstrate equivalent or superior test performance characteristics - analytical validity (AV) and clinical validity (CV) - to established standard-of-care (SOC) methods (i.e., culture, pathogen-specific polymerase chain reaction [PCR]) *for the majority of targets included on the panel*.
 - CV of any new organisms and analytes that are not already established as SOC or that do not have a predicate test that is covered by this contractor must be established through a study published in the peer-reviewed literature for the intended use of the test in the intended population.
- Documentation of the following is clearly stated in the medical record:
 - Specific clinical indications for testing (i.e., clinical suspicion of a pathogen as the cause of the patient's condition)
 - Specific reasons for performing panel testing
 - Provider type/specialty and Place of Service
- Testing must be performed according to Clinical Laboratory Improvement Amendments (CLIA) and/or FDA regulations. For example, CLIA-non-waived tests may only be performed in certified laboratories and according to CLIA regulations. CLIA-waived tests may be performed in healthcare settings that operate under a CLIA Certificate of Waiver or Certificate of Compliance/Certificate of Accreditation. Panels intended for home use (including those that have been FDA approved or cleared) do NOT meet the coverage criteria of this policy.

Non-Coverage Criteria

Molecular Syndromic Panel Tests will NOT be covered in the following circumstances:

- If the test is performed as a test of cure.
- If the patient has been previously tested by molecular diagnostic methods for the same pathogens within 14 days for the same clinical indication.
 - If a previous panel test was performed with a similar/duplicative intended use, a subsequent test is only reasonable and necessary if the non-duplicative content of the second test is reasonable and necessary.
 - Exception: Repeat panel testing for the same clinical indication will only be covered if first panel yielded a negative result AND there is a high index of suspicion for a pathogen as the cause of symptoms AND the patient's clinical condition is not improving or is deteriorating after a clinically appropriate length of time. In such cases, 1 additional panel test may be covered between 1 and 14 days *after* the initial panel test, so long as the test fulfills the criteria for coverage as set forth

in this policy.

LIMITED COVERAGE FOR EXPANDED (>5 Pathogens) PANEL TESTING

FOR THE SPECIFIC PANEL TYPES LISTED BELOW, ALL OF THE FOLLOWING ADDITIONAL CRITERIA MUST BE MET:

- **Respiratory (RP) and Pneumonia (PNP) Panels** will only be covered when targeted testing is not appropriate AND according to the following additional criteria:
 - For immune-competent patients, at least 1 of the following must apply:
 - Testing is ordered by a clinician specialist in Infectious Diseases or Pulmonology for a patient with severe and established underlying respiratory pathology (i.e., severe asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary fibrosis, radiation therapy to the lung) AND treatment with antibiotics may be indicated according to established guidelines.^{1,2} Specific examples that do NOT meet coverage criteria according to established guidelines include the following:
 - Asthma exacerbations without the additional presence of either fever and purulent sputum or radiographic evidence of pneumonia²
 - Uncomplicated community acquired pneumonia (CAP)¹
 - The patient is seriously or critically ill or at imminent risk of becoming seriously or critically ill (as defined by the American Hospital Association's "General Guide for the Release of Information on the Condition of Patients")³ as a result of a presumed respiratory infection AND the patient is being treated in an appropriate critical care facility.
 - For immune-suppressed patients: Testing is ordered by a clinician specialist in 1 of the following: Infectious Diseases, Pulmonology, Oncology, Transplant OR the patient is being managed in an appropriate critical care facility.
 - For ALL patients: Only 1 of the following panels - RP **OR** PNP- will be covered for a given patient for the same clinical indication. The PNP should be prioritized in the evaluation of pneumonia from lower respiratory tract specimens (i.e., bronchoalveolar lavage samples [BALs]). For the purposes of repeat panel testing for the same clinical indication, RP and PNP will be considered as equivalent tests, such that if criteria for repeat testing are met (as defined above), a clinician may choose to perform the repeat test using the PNP, even if the original test was performed using the RP.
 - For ALL patients, exceptions to the limitation on medical specialists who can order expanded panel tests are provided in the accompanying Billing and Coding Article, such that patient geography and access to care do not preclude the receipt of appropriate diagnostic testing when indicated.
- **Gastrointestinal (GI) Panels** will only be covered when targeted testing is not appropriate AND according to the following additional criteria:
 - For immune-competent patients, at least 1 of the following must apply:
 - Testing is ordered by a clinician specialist in Infectious Diseases or Gastroenterology for a patient with severe and established underlying GI pathology (i.e., inflammatory bowel disease (IBD), paralytic ileus, radiation therapy to the intestine) AND identification of an infectious cause is necessary to determine next steps in patient management.
 - The patient is seriously or critically ill or at imminent risk of becoming seriously or critically ill (as defined by the American Hospital Association's "General Guide for the Release of Information on the Condition of Patients")³ as a result of a presumed GI infection AND the patient is being treated in an appropriate critical care facility.
 - The patient's clinical indication for GI panel testing is diarrhea, and ALL of the following apply:
 - The diarrheal illness MUST be acute or persistent with signs or risk factors for severe disease (i.e., fever, bloody diarrhea, dysentery, dehydration, severe abdominal pain) that may warrant hospitalization AND/OR
 - The diarrheal illness is not resolving after 7 days AND the patient has NOT taken laxatives

within 24 hours of the test

- For immune-suppressed patients:
 - Testing is ordered by a clinician specialist in 1 of the following: Infectious Diseases, Gastroenterology, Oncology, Transplant OR the patient is being managed in an appropriate critical care facility.
- For ALL patients, exceptions to the limitation on medical specialists who can order expanded panel tests are provided in the accompanying Billing and Coding Article, such that patient geography and access to care do not preclude the receipt of appropriate diagnostic testing when indicated.
- **Urogenital/Anogenital (UG/AG) Panels**
 - For the UG/AG panels, epidemiologic indication or potential exposure to sexually transmitted pathogens (i.e., in the case of clinical concern for multiple sexually transmitted infections (STIs) due to a high-risk experience) is considered a covered clinical indication, even in the absence of clinical symptoms. Documentation of the high-risk reason for panel testing is clearly stated in the medical record.
 - In the absence of a high-risk experience, if the primary clinical concern is for a few specific pathogens due to specific signs and symptoms (i.e., lesions suggestive of herpes simplex virus [HSV]), then it is expected that only a small targeted panel (i.e., including HSV-1 and HSV-2) will be performed. In such cases, expanded panels are NOT considered reasonable and necessary and will NOT be covered.
 - For the diagnosis of infectious vaginosis/vaginitis, it is reasonable to perform a (targeted or expanded) panel that includes a combination of at least 2 of the following: *Gardnerella vaginalis*, other BV-associated bacteria (BVAB) (such as *Atopobium vaginae* and/or *Megasphaera types*), *Trichomonas vaginalis*, and *Candida* species.
- **Meningoencephalitis (ME) Panels** will be covered according to the following additional criteria:
 - For immune-competent patients: the patient has at least 2 of the following indicators of central nervous system (CNS) infection: cerebrospinal fluid (CSF) markers, radiology, clinical signs and symptoms consistent with meningitis or encephalitis, epidemiologic indication or exposure. For immune-compromised patients, at least 1 of these indicators is required.
 - For all patients: Testing is from a sample collected via lumbar puncture, and NOT an indwelling medical device (i.e., CSF shunts).
- **Bloodstream Infection (BSI) Panels** will be covered according to the following additional criteria:
 - There is clinical concern for bacteremia or sepsis AND microbe(s) were seen on a Gram stain from the patient's blood AND the patient is being managed in an appropriate critical care facility (this includes the Emergency Room), AND
 - Personnel (i.e., an antimicrobial stewardship team [ASP]) are equipped for rapid (within 24 hours) tailoring of antimicrobial therapy as a result of rapid testing.
- **Urinary Tract Infection (UTI) Panels** will be covered according to the following additional criteria:
 - The patient is symptomatic AND at higher risk for UTI complications (i.e., the elderly, patients with recurrent symptomatic UTIs and/or complicated urinary tract anatomy) AND/OR is seen in urogynecology or urology specialty care settings.

Additional information related to specific panels may be found in the related Billing and Coding article.

Tests that demonstrate similar indicated uses and equivalent or superior performance to SOC or other covered tests, as demonstrated in a TA, may similarly be covered under this policy.

Additional syndromic panel types and indications may also be covered according to the established criteria outlined in this policy.

Summary of Evidence

Molecular panel tests for infectious diseases have changed the landscape of clinical microbiology. They play an important role in diagnostic testing, as they simultaneously detect several different pathogens associated with similar

and overlapping clinical symptomatology. For this reason, they are also known as 'syndromic panel' tests. These panels belong to a category of testing known as culture-independent diagnostic tests (CIDTs), which are tests that detect pathogens without the need to grow and isolate them in culture. These tests have shorter turnaround times, often have good test performance characteristics, and require limited technical expertise, making them appealing for use by clinicians as well as clinical laboratories.

Historically, physicians were required to select the specific pathogens most likely thought to be associated with a patient's disease. They often had to rely on empiric therapy until results from the laboratory could be used in identifying definitive or targeted antimicrobial therapy, with results taking days and sometimes weeks. In recent years, molecular panel tests, including multiplex PCR, have become increasingly used for the detection of pathogens, and clinicians are no longer required to name (or separately test for) many of the bacterial, viral, fungal, and parasitic species sought for a given clinical 'syndrome'. As the use of multiplex molecular tests have decreased the need to perform multiple assays to diagnose a given infection, results are often available to the physician within minutes to hours. Though culture-based methods of diagnosis are still routinely utilized, and definitive antimicrobial therapy may still lag pending full culture and susceptibility information, these tests have revolutionized infectious disease diagnostics and have made the road from diagnosis to treatment very rapid, in some cases occurring at the point-of-care (POC).

For some conditions, such as respiratory tract infections, RP panels have become the SOC. These respiratory panels are exceptionally rapid, providing results in minutes to hours.^{4,5} They are unlike the older conventional respiratory viral testing methods such as viral culture and immunofluorescence, which could take days to weeks to obtain a result. Moreover, they display test performance characteristics (sensitivity and specificity) which are often superior to other rapid diagnostic tests for respiratory viruses, such as rapid (antigen-based) influenza detection tests (RIDTs).⁶⁻⁸ For these reasons, many laboratories have stopped offering some of the other diagnostic modalities described for respiratory viral pathogens detection. In fact, many of those methods have become obsolete in routine clinical care.

Finally, some of these multiplex panels are smaller, or 'targeted', detecting just a few pathogens whereas others are very large, detecting approximately 20 targets. The larger panels are sometimes referred to as 'expanded'. These distinctions most commonly apply to the RP and GI panels, as panels for BSI and ME (and in some circumstances UG/AG) are expected to detect >5 pathogens (though a UG/AG panel is not expected to detect as many as 20 pathogens, due to the epidemiology of disease in that organ system). Many commercial platforms for multiplex panel testing have been developed for a variety of infection types in different organ systems.^{4,5} Both smaller and larger panels are being used in clinical laboratories, though their optimal use and application in various settings and for various patient populations and indications remains a challenge.

Test Performance

In recent years, molecular syndromic panels have become routinely used for a number of infection types, including respiratory, gastrointestinal, central nervous system, bloodstream, and urogenital/anogenital. These panels provide rapid turnaround times for results and are often more sensitive than traditional testing for the various organisms included.^{4,5,9} However, test performance characteristics do vary depending on the specific panels and pathogens. For example, though overall sensitivities and specificities have ranged from 84-100% for various RP platforms evaluated, the sensitivities for adenovirus, influenza A H1/2009, and influenza B using the FilmArray® RP have been reported as low as 57%, 73%, and 77%, respectively, while more recent versions of the platform (the FilmArray® RP2) have shown improved detection (94%-100%) of these pathogens.^{10,11} Additionally, the FilmArray® PNP and RP panels have targets in common, though the PNP also contains numerous bacterial targets as well as antimicrobial resistance determinants; the PNP is also semiquantitative.^{12,13} The PNP has shown strong agreement with both SOC methods as well as with the RP in identifying pathogens from lower respiratory tract specimens.^{12,13} Because the PNP performs similarly to the RP for viral pathogens, but can additionally detect bacterial pathogens and antimicrobial resistance determinants, it should be prioritized in the evaluation of pneumonia from lower respiratory

tract specimens.¹⁴ A study comparing the performance of additional RP assays reported the following sensitivities and specificities: 98.3% and 99.2% for GenMark Dx® eSensor® Respiratory Viral Panel (RVP), 92.7% and 99.8% for Luminex® xTAG® RVPv1, and 84.4% and 99.9% for Luminex® xTAG® RVP Fast.¹⁰ In this study, sensitivities also varied by viral target.¹⁰ Smaller targeted panels detecting influenza and respiratory syncytial virus (RSV) have also shown overall high sensitivity and specificity in studies evaluating their performance. A prospective and retrospective evaluation of the Xpert® Flu/RSV XC assay reported sensitivity/specificity of 97.8%/100% and 97.9%/100% for influenza and RSV, respectively.¹⁵ Another study using prospective patient samples reported 96.6%-100% agreement between the ARIES® Flu A/B & RSV and Cepheid® Xpert® Flu/RSV XC assays.¹⁶ This is important, as some of the targeted respiratory panels have been granted CLIA-waived status and are being used in non-laboratory settings.^{17,18} In a study evaluating the Roche cobas® Liat® Influenza A/B & RSV assay performed by nonlaboratory staff, reported sensitivities/specificities were 99.6%/97.5%, 99.3%/99.7%, and 96.8%/98.8% for influenza A, B, and RSV, respectively.¹⁹ Yet another study comparing rapid POC nucleic acid amplification tests (NAATs) found that the sensitivity of Alere™ i was only 71.3% (compared to 100% for the Liat®).²⁰ The poor sensitivity of the Alere™ i in that study was attributed to the inclusion of many low-positive samples.²⁰

The BioFire® FilmArray® and Luminex® xTAG® GI panels demonstrate overall high sensitivity (>90%) for the majority of their targets.²¹ However, sensitivities have been very low for certain targets, specifically *Aeromonas sp.* (23.8%) on the FilmArray® and *Yersinia enterocolitica* (48.1%) on the xTAG®²¹; because of its low sensitivity, *Aeromonas* is not included as a reportable analyte on the cleared version of the FilmArray® test.²² A multicenter study evaluating the FilmArray® GI panel found the sensitivity to be 100% for 12 of the 22 targets and >94.5% for an additional 7 targets (performance of the remaining targets was not assessed due to their low prevalence); specificity was >97.1% for all panel targets.²² In a study comparing the Luminex® xTAG® to conventional methods of testing found that the panel had a higher sensitivity than SOC for detecting *C. difficile*, *Campylobacter* species, norovirus, and rotavirus.²³

The ME panel (the BioFire® FilmArray® ME panel is currently the only commercially available panel) has overall good sensitivity for most targets, but does suffer from a lack of sensitivity for certain targets, such as *Cryptococcus* species, relative to conventional testing methods for this pathogen.²⁴⁻²⁶ In 1 prospective multicenter evaluation, the FilmArray® ME panel showed a percent positive agreement (PPA) with SOC methods of 100% for 9 of 14 analytes, with another 2 analytes showing PPA between 85.7-95.7%; the percent negative agreement (NPA) with SOC methods was >99% for all analytes but *S. agalactiae*.²⁴ Importantly, the ME panel detected 43 pathogens that were not recovered by conventional testing; however, additional testing confirmed the ME panel to be correct in only 43% of these cases.²⁴ In this and other studies, false positive results of the ME panel have been reported, primarily for *S. pneumoniae*, *S. agalactiae*, and HSV-1, and false negatives have been reported primarily for HSV-1 and HSV-2, Enterovirus, and *Cryptococcus neoformans/gattii*.²⁴⁻²⁶ A systematic review and meta-analysis of 13 studies evaluating the ME panel reported a sensitivity and specificity of 90% and 97%, respectively.²⁶

BSI panel tests also show good overall performance. Studies have found the FilmArray® Blood Culture Identification (BCID) panel and the Verigene® (Gram-positive and Gram-negative blood culture) panels provide correct identification for 87%-99% of monomicrobial samples, compared to conventional methods.^{27,28} One study comparing the 2 panel tests to SOC found that the FilmArray® and the Verigene® correctly identified 95% and 99% of isolates, respectively, in monomicrobial cultures.²⁷ False positives and false negatives have been reported in these panels, for both organism and resistance gene identification, particularly in polymicrobial samples; however, the failure to detect organisms in polymicrobial samples is often the result of organisms not included on the panels.^{5,29} Nevertheless, because of limitations inherent in the tests (including the fact that not all organisms are represented on the panels and these are high-stakes infections), both the ME and BSI panel tests must be accompanied by Gram stain and culture.

Molecular panel tests are also increasingly being used for the detection of urogenital and anogenital infections. The BD MAX™ vaginal panel has reported sensitivities and specificities of 89.8%/96.5%, 97.4%/96.8%, and 100%/100%

for bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and trichomoniasis (TV), respectively.³⁰ In another study, the BD Affirm™ VP8 Microbial Identification Test showed a lower specificity of 81.6% for BV and lower sensitivity of 69.4% for VVC, while it performed equally well as the BD MAX™ for TV.³¹ These panels, however, have been shown to perform better than clinician assessment of vaginitis, for which many diagnoses remain empirical and for which guideline non-adherence is broad.³²⁻³⁴ Further, high rates of coinfection with STIs (24.4%-25.7%) have been observed.³⁵⁻³⁷ Panels detecting sexually transmitted pathogens have also become routine in clinical laboratories, as they provide a rapid result for organisms like *Chlamydia* species, that can be difficult to culture. Moreover, it is well-established that *N. gonorrhoeae* and *C. trachomatis* not only cause similar clinical syndromes but also coexist in a significant proportion of patients, highlighting the need for panel testing.³⁸

For the evaluation of UTI, multiplex PCR panels have shown agreement of $\geq 90\%$ with SOC urine cultures for the identification of organisms from urine, though there are currently no United States (U.S.) FDA-approved panels for this indication.^{39,40} Similarly, there are no currently approved panels for use with sterile body fluids other than blood and CSF, though studies evaluating existing panels (such as the BSI panel) with such fluids have shown pathogen detection in cases where SOC cultures were negative, possibly due to the effect of prior antimicrobial therapy.^{41,42} Though testing may require assay optimization for use with 'other' sterile fluid specimens, 1 study found 100% detection of organisms from sterile fluids inoculated into blood culture bottles when tested using BSI panels.⁴³

There are many commercially available multiplex panels for the diagnosis of infectious diseases, and this review of their performance is not inclusive of all of them. As noted in this review, the performance of these panel tests varies, depending on the platform and specimen types used and the targets included. These panel tests should display performance that is equivalent or superior to SOC or other established tests, with *ideal* sensitivity and specificity or PPA and NPA of $\geq 95\%$ for the majority of targets included on their panels. However, it is important to consider the entire picture. For example, as some of these panels are not intended to be used as stand-alone tests, parallel testing by additional methods can be used to support their application in clinical settings, particularly in cases where the assay has not achieved the ideal performance metrics for a given target. Finally, the specific performance limitations of the various panel tests (in some cases due to enhanced sensitivity for targets that may not be pathogenic) must be considered. These issues are further discussed in the **Clinical Utility** section below.

Clinical Utility - Impact on Patient Management and Interpretation of Results

Rapid diagnostics require rapid intervention to be impactful for patient management. Rapid, user-friendly, multiplexed molecular tests have great potential in this regard, though their impact on patient outcomes is clearer for some types of panels, infections, and patients than for others, as studies are variable in design and quality.^{4,5,8,44} A systematic review of the impact of rapid point-of-care testing (POCT) (including molecular assays) for influenza found that, in patients with acute respiratory infection, a positive POCT result significantly increased use of antivirals for influenza and decreased unnecessary antibiotic use.⁴⁵ Another study of adult patients found a decreased time to diagnosis (of influenza and non-influenza viruses) using the FilmArray® RP, compared to conventional methods of testing; moreover, a diagnosis of influenza was associated with lower odds ratio for admission, length of stay (LOS), duration of antimicrobial use, and number of chest x-rays.⁴⁶ Better influenza detection, a reduced LOS, and improved antiviral use were also found in a study of routine molecular POCT for respiratory viruses (the ResPOC study), for adults presenting to the hospital with acute respiratory illness.⁴⁷ However, studies have shown that other factors, such as the presence of infiltrates on chest x-ray and uncertainty regarding the possibility of a bacterial infection, also play a significant role in the decision to treat with antibiotics, regardless of the result of the RP test.⁴⁸ A systematic review of the literature concluded that RPs provide accurate results, and that there is high-quality evidence to support that rapid testing can result in a decreased LOS and can increase appropriate oseltamivir use.⁸ Notably, the majority of RP studies have focused on the benefits in influenza-positive patients. For example, in a study evaluating antimicrobial prescriptions following RP testing among adult outpatients, antibiotic prescription rates were significantly different between patients who tested positive for

influenza virus and those who did not; however, antibiotic prescription rates were not different between the patients who tested positive for viruses other than influenza and those who tested negative.⁴⁹ Since influenza is 1 of the few respiratory infections that can be treated with antivirals, this suggests that a more targeted testing approach is sufficient for most immune-competent patients with a presumed acute viral respiratory infection. Moreover, guidelines on CAP by the Infectious Disease Society of America (IDSA) recommend NOT obtaining testing (specifically sputum Gram stain and culture) routinely in adults with CAP managed in the outpatient setting; rather, they recommend that empiric antibiotic therapy be initiated in adults with clinically suspected and radiographically confirmed CAP, *even if these patients test positive for influenza*.¹ In other words, RP testing does not impact initial management with antibiotics in such circumstances. However, IDSA guidelines do suggest testing for influenza in adult patients with CAP when influenza is circulating in the community.¹ In such cases, a targeted panel for influenza testing can be performed. Finally, specific diagnosis and definitive antimicrobial therapy is needed for pneumonia that is complicated (i.e., by meningitis, endocarditis, or abscess), and testing using expanded panels is warranted in these circumstances; however, these patients are expected to be managed in the inpatient setting.

A more expansive testing approach may be appropriate in patients with underlying pulmonary pathology and in immune-compromised patients, *but only in certain circumstances*. In a study of adult patients with exacerbation of airway disease, 35% of those testing positive for viruses (using molecular POCT) had early discontinuation of antibiotics compared to 13% of those who tested negative and 6% of controls; moreover, of those positive for viruses, only 20% were positive for influenza and the discontinuation of antibiotics was not different between the various viruses detected.⁵⁰ The authors of this study stress that many of the patients in this study should not have been treated with antibiotics, on clinical grounds alone, "given that antibiotic use in patients with asthma exacerbation is strongly discouraged by national society guidelines."^{2,50} The Global Strategy for Asthma Management and Prevention states "evidence does NOT support the role of antibiotics in asthma exacerbations unless there is strong evidence of lung infection (e.g., fever and purulent sputum or radiographic evidence of pneumonia)."² Finally, a study evaluating respiratory virus infections prior to hematopoietic cell transplant (HCT) found that patients with viruses detected pre-HCT had fewer days alive and out of the hospital and lower survival at day 100 than patients with negative results (even when the only virus present was rhinovirus); importantly, most patients in this study were asymptomatic when surveillance samples were collected.⁵¹ This finding suggests that pre-transplant evaluation is 1 limited circumstance in which expanded RP panel testing may be warranted in asymptomatic patients.

Impact studies of GI panels have been even more mixed, though some have found that implementation of such panels was associated with a decrease in endoscopic procedures, abdominal radiology, and/or antibiotic prescriptions.^{52,53} A prospective multi-center study evaluating 1887 fecal specimens from patients with acute diarrhea found that use of a GI panel enhanced organism detection and improved clinical sensitivity, and enabled clinicians to provide more timely and targeted antimicrobial therapy; moreover, positive Shiga-like toxin producing *E. coli* (STEC) results led to the appropriate discontinuation of antimicrobials in the majority of cases when empiric therapy had been initiated.⁹ However, in outpatients with uncomplicated diarrhea that is likely to be self-limited, testing is often not warranted.⁵ Guidelines from the American College of Gastroenterology regarding acute diarrheal infections in adults state that diagnostic studies may be used in cases of "dysentery, moderate-to-severe disease, and symptoms lasting >7 days to clarify the etiology of the patient's illness and enable specific directed therapy."⁵⁴ Regarding the use of the GI panel in special populations, an impact study in patients with IBD found that GI panel testing led to lower rate of IBD treatment modification.⁵⁵ In outpatients with relapse of IBD, testing with a GI panel was associated with significantly lower rates of IBD therapy escalation and endoscopy, compared to patients who underwent conventional testing.⁵⁶ Finally, in a study evaluating gastrointestinal infections prior to HCT in asymptomatic patients found that 62% of patients colonized with *C. difficile* pre-transplantation developed a clinical *C. difficile* infection post-transplantation, and 80% of patients colonized with enteropathogenic *Escherichia coli* (EPEC) or enteroaggregative *E. coli* developed clinical infections due to their colonizing pathogen post-transplantation.⁵⁷ As noted above with respiratory infections, these findings suggest that pre-transplant evaluation is 1 limited circumstance in which expanded GI panel testing may be warranted in asymptomatic patients.

Bloodstream and CNS infections are emergency situations that can progress rapidly, even in previously healthy individuals.⁵⁸ As such, rapid panel testing can prove invaluable in the prompt management of patients with such infections. The following widely cited statistic is sobering – in sepsis, for each hour of delay in *effective* (appropriate for a given pathogen) antimicrobial administration, there is an average decrease in patient survival of approximately 8%.⁵⁹ Because bacterial culture and full antimicrobial susceptibility results traditionally take 2 or more days, rapid BSI panels have emerged to rapidly (within hours) identify a causative pathogen such that the most appropriate and targeted antibiotics can be administered. A prospective randomized controlled trial found that use of a BSI panel resulted in a decrease in time between Gram stain to microorganism identification by approximately 21 hours.⁶⁰ Moreover, the use of broad-spectrum antibiotics and the treatment of bloodstream contaminants were reduced; further, antimicrobial de-escalation occurred with the additional intervention by the ASP.⁶⁰ Other studies have similarly shown more rapid organism identification and antimicrobial de-escalation with the use of BSI panel (plus ASP intervention) over conventional culture methods, even if the latter also included ASP.⁶¹ However, the effect of BSI panels on other outcome measures such as mortality, 30-day readmission, and LOS has been more variable between studies.^{5,61} Pre-post intervention studies⁶² as well as a meta-analysis⁶³ have shown that rapid molecular diagnostic testing is associated with significant decreases in LOS and mortality risk, *particularly when combined with an ASP*. For patients with multi-drug resistant bacteria, rapid *escalation* of antimicrobial therapy is also important. In 1 study, use of a BSI panel decreased the mean time to appropriate antimicrobial therapy by more than 30 hours in a study of patients with vancomycin-resistant enterococci (VRE) bacteremia.⁶⁴ In another, more rapid implementation of effective therapy was observed in cases of extended-spectrum beta-lactamase-producing organisms, but not overall; this same study reported a significantly decreased length of intensive care unit (ICU) stay, 30-day mortality, and mortality associated with multidrug-resistant organisms after the implementation of a BSI panel.⁶² There are fewer outcome studies evaluating the clinical utility of ME panels, particularly for patients generalizable to the Medicare population. One study found that use of the FilmArray® ME panel reduced time to diagnosis by approximately 3 days, allowed an earlier discontinuation of empiric therapy in 32% of patients, and led to an earlier hospital discharge in 18%, saving 82 hospital days.⁶⁵ Another study found that use of the panel significantly reduced the turnaround time for HSV detection, days of therapy for antivirals (acyclovir) and antimicrobials, and hospital LOS, in adults undergoing a lumbar puncture for a suspected community-onset CNS infection.⁶⁶

Results from molecular panel tests must be interpreted with caution. First, they detect significantly more pathogens than were detected in the past using conventional methods of testing.^{5,9} For example, studies evaluating multiplex urine panels (UPs) have detected up to 26% additional organisms that culture methods did not.³⁹ Importantly, multiplex UPs have detected more organisms in polymicrobial infections than urine cultures in symptomatic patients,^{39,67} and a modeling study has shown bacterial combinations that increase the probability of antibiotic resistance.⁶⁸ As with all such panel tests, it is important to determine whether these additional organisms detected are pathogens or colonizers that simply could not be detected before, using traditional SOC methods. As these tests detect microbial nucleic acid, they do not require live and actively replicating organisms. Therefore, not all positive results indicate current active infection. However, in 1 study of 150 urogynecology patients, standard urine culture missed 50% of uropathogens in patients with severe urinary symptoms; moreover, approximately 40% percent of patients with missed uropathogens reported no symptom resolution after treatment based on standard urine culture results.⁶⁹ Importantly, all of the missed uropathogens were detected using the study's comparator method (an enhanced quantitative culture technique), though additional bacteria of unknown pathogenicity were also detected.⁶⁹

Asymptomatic carriage and prolonged shedding (days to weeks) of viral nucleic acid are common, particularly for respiratory and GI pathogens. In BIG-LoVE, a study of 108 adults and children who underwent weekly respiratory panel testing for a year, approximately half of all viral detection episodes were asymptomatic.⁷⁰ Further, PCR detection of viruses at ≥ 3 weeks was a fairly frequent finding, occurring in 16% of episodes; prolonged viral detection was particularly common in children and in individuals living with children.⁷⁰ Prolonged shedding is also common in immune-compromised patients.⁷¹ On the GI panels, interpretation of a positive *C. difficile* result in a patient without risk factors for infection with this organism can be difficult, as 4%-15% of healthy adults, and up to 21% of those admitted to a hospital, are asymptotically colonized; moreover, detection by PCR does not indicate

active infection, particularly in patients without classic clinical symptoms.^{72,73} The high rate of mixed infections observed when using expanded RP (in 30%-40% of positive cases)^{74,75} and GI panels (up to 27% of positive cases)^{5,21-23} can be difficult to interpret. The significance of previously unidentified organisms in stool samples (such as Sapovirus and Astrovirus) can also be clinically challenging to interpret, as it is unclear whether detection of these organisms represents colonization or infection. Mixed infections detected by GI panels most commonly occur with enteropathogenic *E. coli*, *Y. enterocolitica*, Norovirus, and *C. difficile*.^{9,21,53} Moreover, in some studies with very high rates of observed *C. difficile* there are also high rates of inappropriate GI panel testing. In 1 study evaluating more than 440 GI panels at a community hospital, 61% of the panels ordered were deemed inappropriate, for reasons including lack of documented diarrhea, laxative use, and having a duplicate *C. difficile* PCR test ordered.⁵³ Notably, in this study, rates of *C. difficile* were 51%.⁵³

ME and BSI panels also have their own challenges. For example, though co-infections are less commonly observed with multiplex panel testing from sterile body sites (such as from CSF or blood), they do occur and can cause interpretive challenges.²⁴ Additionally, the ME panel cannot differentiate active from latent infection. It detects certain organisms, such as human herpesvirus 6 (HHV-6) and cytomegalovirus (CMV), that may be latent and not the causative agents of disease, particularly if the host is immunocompetent. Moreover, there are a number of organisms that can cause meningitis and encephalitis that are not included on the panel, including bacteria (such as non-K1 *E. coli* serotypes and non-encapsulated strains of *Neisseria meningitidis*), viruses (including arboviruses), and *Mycobacterium tuberculosis*. Therefore, there are significant limitations associated with the use of this panel; however, these are mitigated, in part, by a requirement for additional testing (i.e., bacterial culture, cryptococcal antigen) to occur in parallel, as well as by clinician education and laboratory stewardship. It is important to remember, however, that traditional means of diagnosing CNS infections also come with diagnostic challenges that can delay a diagnosis. Such challenges include the low sensitivity of CSF culture (particularly in patients with antimicrobial exposure prior to lumbar puncture)⁷⁶ as well as the historically unrecognized etiology in most cases of encephalitis.⁷⁷ The large nature of the panels may cause an ordering clinician to assume that, because so many organisms are being tested, a negative result makes infection a less likely cause of the patient's symptoms. Therefore, it is important for clinicians to realize that, even in expanded syndromic panels, not all pathogens will be detected. New strains of viruses may also go undetected, and the panels are limited to only those organisms found on the 'menu'. Though the ME panel cannot fully replace current assays, it can provide unparalleled rapid results for a syndrome that can be rapidly fatal. Similarly, BSI panels are limited by the targets available on the panels, both for identification of microbes as well as identification of genes responsible for resistance mechanisms. In fact, many Gram-negative organisms harbor resistance mechanisms not encoded by any genes on these BSI panels, adding another diagnostic hurdle to overcome. However, they do tend to detect the most common bloodstream pathogens and can provide rapid results for rapid targeted antimicrobial therapy.^{4,5,60}

Additional Challenges and Appropriate Use of Panel Tests

With few exceptions, the FDA-approved molecular panels for a given platform are 'fixed', i.e., they consist of a predetermined test menu of pathogens. The smaller of these tests, sometimes referred to as 'targeted panels', typically detect about 3-5 pathogens. The commonly used commercially available larger, or 'expanded', panels detect approximately 20 targets or pathogens, and some include pathogens that typically cause different clinical presentations, such that simultaneously testing for these pathogens should not be a common event. In other words, they deviate from being 'syndromic' in their approach to diagnosis. For example, the classic infection associated with *Bordetella pertussis* is whooping cough. The clinical case definition of a probable case of pertussis is a cough illness lasting at least 2 weeks, *in the absence of a more likely alternate diagnosis or epidemiologic linkage*, and 1 of the following symptoms: paroxysms of coughing, inspiratory whoop, post-tussive emesis, or apnea.⁷⁸ Though some individuals (such as those with a history of prior infection or vaccine-induced immunity) may not show classic manifestations or may be altogether asymptomatic,⁷⁹ diagnosis of this organism generally should require a high index of suspicion. Although it is a respiratory infection, in most patients, the clinical presentation of whooping cough is unlike that of most other viral respiratory syndromes. Yet, it is included on many respiratory syndromic panels and a patient who is likely infected with influenza or RSV may still end up being tested for *B. pertussis*, simply because it

is a target on a fixed panel. Finally, the targets and organisms on a panel can vary between manufacturers, with some panels differentiating among numerous subtypes and strains of species, many of which are not clinically meaningful for the majority of patients.⁵ For example, differentiating among the different types and subtypes of parainfluenza virus may be good for epidemiologic tracking, but is not likely to result in any meaningful impact to patient care.

Further, large (fixed) panels do not appropriately regard patient risk factors, or a pre-test probability of a particular pathogen causing infection. The patient's medical history and exposures are important to assess prior to testing. For example, infection with *Clostridioides difficile* (formerly known as *Clostridium difficile*) is typically associated with specific risk factors including exposure to antimicrobials, healthcare facilities and hospitals, chemotherapy, and GI procedures.⁸⁰ Conversely, many of the other pathogens on the panels are typically associated with foodborne transmission.^{81,82} Variables like season and geography are also pertinent to a specific diagnostic case or patient. In the case of respiratory panels, a patient can be tested for more than 20 pathogens, when in fact only a couple of viruses may be the predominant ones circulating in the community during a given season. For example, though influenza can circulate throughout the year, it primarily occurs and peaks during the winter months, whereas certain other viruses are more prevalent during other seasons.⁸³ Fixed panels may also not be applicable across populations, and immune-competent patients who are not severely ill may not require testing at all, or may require limited testing.⁸⁴ Viral infections in immune-competent patients are often self-limiting and resolve without complication. Further, with few exceptions, there is often no specific treatment for viral infections, other than supportive care, and testing may not change patient management. All of this may result in an excess of unnecessary testing in immune-competent individuals. On the other hand, in immune-compromised patients, common and rare pathogens can cause severe illness, and concurrent infection with multiple respiratory viruses (which occur more commonly than previously thought, thanks to these multi-analyte panels) have been identified as predictors of in-hospital mortality.⁸⁵ Moreover, immune-compromised patients often do not present with classic symptoms of infection. Therefore, casting a wider diagnostic net for this population may be both reasonable and necessary.

However, even in immune-competent individuals, expanded panels can provide rapid, highly impactful, and epidemiologically important information.⁸⁶ They can lead to the diagnosis of some infections that, in the past, may have been missed altogether. In 1 study, 75% of *Mycoplasma pneumoniae* infections were unintentionally detected by multiplex PCR; in this study, clinicians had only specifically requested testing for *M. pneumoniae* in 2 (10%) of 20 patients positive for this pathogen.⁸⁷ Importantly, this was an actionable finding, as infection with *M. pneumoniae* is treatable with antibiotics.⁸⁷ Expanded panels can also help rapidly diagnose and, in some cases, avert public health outbreaks. For example, during an outbreak of a 'mystery' respiratory illness among children in 2014, hospitals were able to rapidly identify the presumptive cause, which turned out to be enterovirus D68.⁸⁸ Similarly, use of rapid multiplex GI panels significantly contributed to the recognition of a large *Cyclospora* outbreak in 2018.⁸⁹

For all these reasons, instituting the appropriate use of these panels can be challenging. Notably, these tools do not necessarily replace certain conventional methods of microbial detection, such as bacterial and fungal culture, in the diagnosis of infection. These many challenges and opportunities have led to the implementation of measures to promote diagnostic stewardship. Some of these include limiting expanded syndromic panels to certain groups of patients, such as the immune-compromised, hospitalized, critically ill, or patients from specialty clinics (such as pulmonary for respiratory panels). Others include the implementation of test ordering algorithms and 'controls', decision support tools, and the prohibition of repeat testing within a specific timeframe.^{5,53,90,91}

Summary of Contractor Advisory Committee (CAC) Meeting

A multi-jurisdictional CAC Meeting to discuss the clinical literature related to Molecular Diagnostic Testing for Pathogens took place on Monday, January 11, 2021. The general consensus from the CAC panel is that there is accuracy and reliability in these pathogen panels and that the results from panel testing may improve patient health outcomes. However, the CAC panel also noted that outcome studies from use of these panels is limited, depending

on the specific panel (and use) in question. The panel emphasized the importance of regarding patient population and setting, as indications for testing can vary among beneficiaries with different medical backgrounds and needs, and highlighted differences in testing requirements between immune-compromised and immune-competent patients. Overall, the panel expressed that a key consideration is whether a result is going to positively impact patient care. Finally, there was consensus from the CAC participants that the use of this technology in the diagnosis of onychomycosis (fungal infections) of the nail was unnecessary.

Analysis of Evidence (Rationale for Determination)

The goal of diagnostic stewardship is to select the right test for the right patient at the right time, to optimize patient care.⁹² The evidence shows that molecular syndromic panels for infectious disease testing can result in prompt patient management, including the rapid initiation of appropriate antimicrobial therapy, the timely de-escalation of therapy, and the decrease in unnecessary therapy. In some cases, these panels have resulted in additional improvements in overall care, including a decrease in the use of unnecessary diagnostic procedures and even a decrease in LOS, morbidity, and mortality. Moreover, infectious disease testing has traditionally relied on testing for multiple organisms when a physician was unsure of the pathogen causative of a presumed infectious disease. Historically, this investigation was performed *using multiple different tests and/or culture (which also detects multiple different organisms using agar plates)*. In this regard, panel testing can be thought of as the use of new methodology (i.e., multiplex NAAT) for the detection of many of the same clinically valid pathogens that were historically detected using combinations of SOC methods (culture, antigen testing, etc.). Importantly, these SOC methods also suffer from significant limitations. For all these reasons, such panel tests are considered reasonable and necessary.

However, the implementation of syndromic panels has also been a challenge, as these panels detect a fixed number of organisms, not all of which are appropriate for a given patient or setting, or during a given season. Some of these pathogens may, in fact, be extremely rare and not be appropriate for a patient's medical history and clinical symptoms. Further, infections with some of the organisms included on the panels are self-limited and their detection may not change management. In such cases, testing is not required.^{5,18} Finally, despite their many advantages including diagnostic speed, expanded syndromic panels have shown limited clinical utility for routine use in general populations. There is not a common circumstance in the outpatient setting for which it is reasonable and necessary to perform *expanded* panel testing. Rather, the clinical utility of expanded panels is most evident for select indications, populations, and settings such as immune-compromised and hospitalized patients. On the other hand, smaller targeted panels are more applicable to broader populations and have a broader role in the routine testing of immune-competent beneficiaries.

Additionally, while there is no evidence to suggest that a specific number of pathogens is required for inclusion in limited and expanded panels, the selected cutoff of <5 pathogens for limited panels and ≥ 6 for expanded panels is based on the following: 1. CPT® codes for such panel tests are listed according to number of *targets*, 2. The distinction between limited and expanded panel testing is a conventional distinction used in the field, particularly for the RP and GI panels, 3. In clinical medicine, a typical differential diagnosis usually includes the top 3-5 diagnoses for most indications for otherwise healthy populations, and is therefore aligned with such a distinction in testing, and 4. A single pathogen in the clinical sense (i.e., 'Influenza') may have multiple types that require testing by the laboratory (i.e., Influenza testing, at a minimum, should include targets for Influenza A and B), rendering this type of test a 'panel' if used with even 1 additional pathogen, such as RSV. While we would prefer to focus solely on relevant pathogens in different patient settings and indications, based on the literature and feedback of the CAC this is currently quite difficult; additionally, the field has settled on a distinction between smaller targeted panels and larger 'syndromic' panels. We will subsequently consider this distinction for the time being in this policy until such time that the distinction is no longer necessary. For these reasons, we believe in the general Medicare population that, for most indications, only smaller targeted tests are reasonable and necessary outside of immune-compromised patients and other limited special circumstances, as outlined in this policy and in the related Billing and Coding article. It is important that testing is guided by the evidence in consideration of which patients will truly benefit. At present, acceptable thresholds for coverage have been met for a number of molecular syndromic infectious disease panels.

This contractor will continue to assess the evidence for coverage for additional panel types and indications, according to the criteria outlined in this policy.

Finally, the landscape of infectious disease diagnostics is rapidly evolving such that currently covered tests may become obsolete as new pathogens and methodologies become important for testing. One example is metagenomic testing for infectious diseases. Unlike panel tests, which identify fixed organisms on a panel, this technology may further revolutionize the field with its high-throughput capacity, rapid results, and the ability to simultaneously identify all organisms present in a sample.⁹³⁻⁹⁷ This contractor will continue to monitor the evidence, and new developments that may impact this coverage decision.

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
04/17/2022	R1	Posted 04/28/2022 Under Bibliography 3. Broken link removed.	<ul style="list-style-type: none"> Other (Review/Broken link correction)

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

[A58761 - Billing and Coding: MoIDX: Molecular Syndromic Panels for Infectious Disease Pathogen Identification Testing](#)

[DA58761 - Billing and Coding: MoIDX: Multiplex Nucleic Acid Amplification Test \(NAAT\) Panels for Infectious Disease Testing](#)

[A59020 - Response to Comments: MoIDX: Molecular Syndromic Panels for Infectious Disease Pathogen Identification Testing](#)

LCDs

[DL39044 - MoIDX: Multiplex Nucleic Acid Amplification Test \(NAAT\) Panels for Infectious Disease Testing](#)

Related National Coverage Documents

N/A

Public Versions

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- Molecular Syndromic Panels for Infectious Disease Pathogen Identification Test
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