PHP_2.04.10	Identification of Microorganisms Using Nucleic Acid Probes		
Original Policy Date:	March 1, 2026	**Effective Date:**	March 1, 2026
Section:	2.0 Medicine	**Page:**	Page 1 of 55

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. Department of Health Care Services (DHCS) Provider Manual Guideline:
- TAR and Non-Standard Benefits List: Codes 0001M thru 0999U (tar and non cd0)
- TAR and Non-Standard Benefits List: Codes 80000 thru 89999 (tar and non cd8)
- Pathology: Microbiology (path micro)
- Proprietary Laboratory Analyses (PLA) (prop lab)

Below is an excerpt of the PLA guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Requirements for PLA code 0588U (e.g., TriVerity™):
A Treatment Authorization Request (TAR) requires documentation of all of the following criteria:
- Member is 18 years of age or older, and
- Test must be ordered by emergency department clinician, and
- Management will be contingent on test results, and
- Member presents to the emergency department with one of the following:
  - Suspected sepsis, or
  - Suspected acute infection and at least one abnormal vital sign.

- Laboratory Services (lab)

Below is an excerpt of the guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Requirements for CPT code 87529:
- **Usage Restrictions**: Only as necessary to evaluate genital ulcers of unconfirmed etiology. Limited to Herpes

Requirements for CPT code 87535:
- **Usage Restrictions**: Only when HIV-1/HIV-2 differentiation assay results are negative or indeterminate

Requirements for CPT code 87563:
- **Usage Restrictions**:
  - This test is intended for use as a diagnostic test for recurrent urethritis, cervicitis, and in some cases of Pelvic Inflammatory Disease (PID). It is not a covered benefit when used and billed as a screening test in asymptomatic persons

- This test is intended for use as a diagnostic test for recurrent urethritis and epididymitis. It is not a covered benefit when used and billed as a screening test in asymptomatic persons

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:
- N/A

Policy Statement

Any criteria that are not specifically addressed in the above Provider Manual, please refer to the criteria below.

I. The use of nucleic acid testing using a direct or amplified probe technique (*without* quantification of viral load) may be considered **medically necessary** for **any** of the following microorganisms (see Policy Guidelines):
   A. Bartonella henselae or quintana
   B. Bordetella pertussis
   C. Candida species
   D. Chlamydia pneumoniae
   E. Chlamydia trachomatis
   F. Clostridium difficile
   G. Enterococcus, vancomycin-resistant (e.g., enterococcus vanA, vanB)
   H. Enterovirus
   I. Herpes simplex virus ***(Per Medi-Cal guidelines and for Medi-Cal members only: please see criteria for CPT code 87529 in the State Guidelines section above.)***
   J. Human papillomavirus
   K. Influenza virus
   L. Legionella pneumophila
   M. Mumps
   N. Mycobacterium species
   O. Mycobacterium tuberculosis
   P. Mycobacterium avium-intracellulare
   Q. Mycoplasma genitalium (MG) ***(Per Medi-Cal guidelines and for Medi-Cal members only: please see criteria for CPT code 87563 in the State Guidelines section above.)***
   R. Mycoplasma pneumoniae
   S. Neisseria gonorrhoeae
   T. Rubeola (measles)
   U. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
   V. Staphylococcus aureus
   W. Staphylococcus aureus, methicillin-resistant
   X. Streptococcus, group A
   Y. Streptococcus, group B
   Z. Trichomonas vaginalis
   AA. Zika virus

II. The use of nucleic acid testing using a direct or amplified probe technique (*with or without* quantification of viral load) may be considered **medically necessary** for **any** of the following microorganisms:
   A. Cytomegalovirus
   B. Hepatitis B virus
   C. Hepatitis C virus
   D. HIV-1 ***(Per Medi-Cal guidelines and for Medi-Cal members only: please see criteria for CPT code 87535 in the State Guidelines section above)***

   E. HIV-2
   F. Human herpesvirus 6

III. The use of nucleic acid testing with quantification of viral load is considered **investigational** for microorganisms that are not included in the list of microorganisms for which probes with or without quantification are considered medically necessary.

IV. The use of nucleic acid testing using a direct or amplified probe technique is considered **investigational** for the following microorganisms:
   A. Gardnerella vaginalis
   B. Hepatitis G

V. Respiratory viral panel testing in the outpatient setting may be considered **medically necessary** when **BOTH** of the following criteria have been met:
   A. Use of limited panels involving 5 targets or less
   B. The results of testing will be used to guide or alter management

VI. Respiratory viral panel testing in the outpatient setting is considered **investigational** when using large panels involving 6 or more targets.

VII. The use of the following nucleic acid testing panels (*with or without* quantification of viral load for viral panel elements) is considered **investigational**:
   A. Central nervous system pathogen panel
   B. Gastrointestinal pathogen panel
   C. Urogenital pathogen panel

Policy Guidelines

For the purposes of this policy, other than the respiratory pathogen panel, gastrointestinal pathogen panel, and central nervous system panel, nucleic acid testing for individual organisms is informed by published guidelines and is not subject to evidence review (see Supplemental Information). Many probes have been combined into panels of tests. Multi-target tests are commercially available and some are U.S. Food and Drug Administration (FDA) cleared (e.g., Alinity mSTI). The FDA maintains a list of 'Cleared or Approved Nucleic Acid Based Tests' at https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. New tests may become available between policy updates.

Vaccine-preventable disease surveillance for outbreaks and diagnosis of isolated cases: the Centers for Disease Control and Prevention (CDC) Pertussis and Diphtheria Laboratory has developed its own polymerase chain reaction (PCR) and serological assays to diagnose pertussis, mumps, and rubeola (measles) and has recommendations for their appropriate use.

For *Candida* species, culture for yeast remains the criterion standard for identifying and differentiating these organisms. Although sensitivity and specificity are higher for nucleic acid amplification tests (NAATs) than for standard testing methods, the CDC and other association guidelines do not recommend NAATs as first-line testing for *Candida* species. The CDC (2015) classifies uncomplicated vulvovaginal candidiasis as being sporadic or infrequent; or mild to moderate; or, in non-immunocompromised individuals, as likely to be caused by *C. albicans*. A presumptive diagnosis can be made in the clinical care setting. However, for complicated infections, the CDC states that NAATs may be necessary to test for multiple *Candida* subspecies. Complicated vulvovaginal candidiasis is classified as being recurrent or severe; or, in individuals with uncontrolled diabetes, debilitation, or immunosuppression, as less likely to be caused by a *C. albicans* species.

Antibiotic sensitivity of streptococcus A culture is generally not performed for throat cultures. However, if an antibiotic sensitivity is considered, then the most efficient method of diagnosis would be a combined culture and antibiotic sensitivity.

In the evaluation of group B streptococcus, the primary advantage of a DNA probe technique compared with traditional culture techniques is the rapidity of results. This advantage suggests that the most appropriate use of the DNA probe technique is in the setting of impending labor, for which prompt results could permit the initiation of intrapartum antibiotic therapy.

Use of NAAT for SARS-CoV-2 is for confirming coronavirus disease 2019 (COVID-19) diagnoses. This medical policy does not address antibody testing (serological IgG assays).

It should be noted that the technique for quantification includes both amplification and direct probes; therefore, simultaneous coding for both quantification with either amplification or direct probes is not warranted.

Large viral panels, which contain 6 or more pathogen targets, often include uncommon clinical viral targets. These pathogens are either unlikely to be found in the populations being tested or, if identified, do not change the management of the patient. There is a lack of evidence supporting the use of large viral panels over limited viral panels (those with 5 or fewer pathogen targets) in outpatient settings, including emergency departments and for non-hospitalized individuals under observation care.

Many probes have been combined into panels of tests. For the purposes of this policy, other than the respiratory pathogen panel, gastrointestinal pathogen panel, and central nervous system panel, only individual probes are reviewed.

Coding

See the Codes table for details.

Description

Nucleic acid probes are available for the identification of a wide variety of microorganisms. Nucleic acid probes can also be used to quantitate the number of microorganisms present. This technology offers advantages over standard techniques when rapid identification is clinically important, microbial identification using standard culture is difficult or impossible, and/or treatment decisions are based on quantitative results.

Summary of Evidence

For individuals who have signs and/or symptoms of meningitis and/or encephalitis who receive a nucleic acid-based central nervous system (CNS) pathogen panel, the evidence includes a systematic review and a pivotal prospective study. Relevant outcomes include test accuracy and validity, other test performance measures, medication use, symptoms, and change in disease status. Access to a rapid method that can simultaneously test for multiple pathogens may lead to the faster initiation of more effective treatment and conservation of cerebrospinal fluid (CSF). The available CNS panel is highly specific for the included organisms, but the sensitivity for each pathogen is not well-characterized. More than 15% of positives in the largest clinical validity study were false-positives. A negative panel result does not exclude infection due to pathogens not included in the panel. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have signs and/or symptoms of gastroenteritis who receive a nucleic acid-based gastrointestinal (GI) pathogen panel, the evidence includes prospective and retrospective evaluations of the tests' sensitivity and specificity and prospective studies on utility. Relevant outcomes include test accuracy and validity, other test performance measures, medication use, symptoms, and change in disease status. The evidence suggests that pathogen panels are likely to identify both bacterial and viral pathogens with high sensitivity, compared with standard methods. Access to a rapid method for etiologic diagnosis of infections may lead to more effective early treatment and infection control measures. However, in most instances, when a specific pathogen is suspected, individual tests could be ordered. There may be a subset of patients with an unusual presentation who would warrant testing for a panel of pathogens at once, but that subset has not been well defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have signs and/or symptoms of respiratory infection who receive a nucleic acid-based respiratory pathogen panel, the evidence includes systematic reviews, 3 randomized controlled trials (RCTs), and a quasi-RCT. Relevant outcomes include test accuracy and validity, other test performance measures, medication use, symptoms, and change in disease status. One systematic review reported that all 3 reviewed multiplex polymerase chain reaction systems were highly accurate. Three RCTs and 1 quasi-RCT evaluated utility of a respiratory panel and found benefits in time-to-treat, targeted antibiotic prescriptions, and length of hospital stay. In addition, 1 subanalysis found fewer antibiotics being prescribed for patients diagnosed with the panel. The panel did not significantly affect duration of antibiotic use, readmission, or mortality rates. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
Not applicable.

Related Policies

- N/A

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

Regulatory Status

The U.S. Food and Drug Administration maintains a list of nucleic acid amplification tests (NAATs) that have been cleared by the Center for Devices and Radiological Health. These NAATs have been cleared for many of the microorganisms discussed in this review and may be reviewed on this site.

Table 1 summarizes the NAATs cleared for central nervous system panels when diagnosing meningitis and/or encephalitis, for panels when diagnosing gastroenteritis, and for respiratory panels.

Table 1. FDA Cleared Nucleic Acid Amplification Tests for Central Nervous System, Gastrointestinal, and Respiratory Panels

NAAT	Manufacturer	510(k) Number	Product Code
Meningitis/Encephalitis (CNS) Pathogen Panels			
FilmArray Meningitis/Encephalitis Panel	BioFire Diagnostics, LLC (Salt Lake City, UT)	DEN150013, K160462	PLO
BioFire Global Fever Panel	BioFire Defense, LLC (Salt Lake City, UT)	K220870	QMV
BIOFIRE FILMARRAY Tropical Fever (TF) Panel	BioFire Diagnostics, LLC (Salt Lake City, UT)	K243463	QMV
Gastroenteritis Pathogen Panels			
xTAG Pathogen Panel (GPP)	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	DEN130003, K121454	PCH
PANNAT STEC Test	Micronics, Inc. (Redmond, WA)	K173330	PCH
Progastro SSCS Assay	Gen-Probe Prodesse, Inc (Waukesha, WI)	K123274	PCH
Biocode Gastrointestinal Pathogen Panel (GPP)	Applied Biocode (Santa Fe Springs, CA)	K180041, K242877	PCH
Biocode Pathogen Panel	Applied Biocode (Santa Fe Springs, CA)	K190585	PCH
EntericBio Dx Assay	Serosep, Ltd (Annacotty, IE)	K182703	PCH
Filmarray Panel	BioFire Diagnostics, LLC (Salt Lake City, UT)	K140407, K160459	PCH
ProGastro SSCS	Hologic/Genprobe (Waukesha, WA)	K123274	PCH
BD MAX Enteric Bacterial Panel (EBP)	BD Diagnostics (Sparks, MD)	K170308	PCH
BD MAX Enteric Viral Panel (EVP)	BD Diagnostics (Sparks, MD)	K181427, K220607	PCH
Verigene Enteric Pathogen Panel (EP)	Nanosphere, Inc (Northbrook, IL)	K142033, K140083	PCH
xTAG Gastroenterology Pathogen Panel (GPP) Multiplex Nucleic Acid-Based Assay System	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	K121894	PCH
FilmArray GI Panel	BioFire Diagnostics, Inc (Salt Lake City, UT)	K140407	PCH
Great Basin Stool Bacterial Pathogens Panel	Great Basin Scientific, Inc. (Salt Lake City, UT)	K163571	PCH
BIOFIRE FILMARRAY Gastrointestinal (GI) Panel Mid	BioFire Diagnostics, Inc (Salt Lake City, UT)	K243885	PCH
QIAstat-Dx Gastrointestinal Panel 2	QIAGEN GmbH (Germantown, MD)	K220062	PCH
QIAstat-Dx GI Panel 2 Mini B&V	QIAGEN GmbH (Germantown, MD)	K243813	PCH
BD MAX Enteric Parasite Panel (EPP)	Becton, Dickinson and Company	K220193	PCH
Respiratory Viral Panels			
Curetis Unyvero Lower Respiratory Panel	Opgen		
BIOFIRE SPOTFIRE Respiratory (R) Panel	BioFire Diagnostics, Inc (Salt Lake City, UT)	K213954	QOF
BIOFIRE SPOTFIRE Respiratory (R) Panel Mini	BioFire Diagnostics, Inc (Salt Lake City, UT)	K230719	QOF
BIOFIRE SPOTFIRE Respiratory/Sore Throat	BioFire Diagnostics, Inc (Salt Lake City, UT)	K232954	QOF
QIAstat-Dx Respiratory Panel; QIAstat-Dx Analyzer	QIAGEN GmbH (Germantown, MD)	K183597	OCC
ID-TAG Respiratory Viral Panel Nucleic Assay System	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	DEN070013, K063765	OCC

NAAT	Manufacturer	510(k) Number	Product Code
Biocode Respiratory Pathogen Panel	Applied BioCode, Inc. (Santa Fe Springs, CA)	K192485	OCC
Nxtag Respiratory Pathogen Panel	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	K193167	OCC
NxTAG Respiratory Pathogen Panel v2 (NxTAG RPP v2)	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	K231758	QOF
xTAG Respiratory Virus Panel (RVP)	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	K081483	OCC
Qiastat-Dx Respiratory Panel	QIAGEN GmbH (Germantown, MD)	K183597	OCC
xTAG Respiratory Virus Panel FAST	Luminex Molecular Diagnostics, Inc (Toronto, Ontario, CA)	K103776	OCC
eSensor® Respiratory Virus Panel (RVP)	Clinical Micro Sensors, Inc (Carlsbad, CA)	K113731	JJH
Verigene Respiratory Pathogens Plus Nucleic Acid Test	Nanosphere, Inc (Northbrook, IL)	K103209	OCC
BioFire FilmArray Respiratory Panel (RP)	BioFire Diagnostics, Inc (Salt Lake City, UT)	K123620	OCC
BioFire FilmArray Pneumonia Panel (BFPP)	BioFire Diagnostics, Inc (Salt Lake City, UT)	K243222	QDS

CNS: central nervous system; DEN: de novo; FDA: Food and Drug Administration; NAAT: nucleic acid amplification tests.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

Background

Nucleic Acid Probes

A nucleic acid probe is used to detect and identify species or subspecies of organisms by identifying nucleic acid sequences in a sample. Nucleic acid probes detect genetic materials, such as RNA or DNA, unlike other tests, which use antigens or antibodies to diagnose organisms.

The availability of nucleic acid probes has permitted the rapid direct identification of microorganism DNA or RNA. Amplification techniques result in exponential increases in copy numbers of a targeted strand of microorganism-specific DNA. The most used amplification technique is polymerase chain reaction (PCR) or reverse transcriptase PCR. In addition to PCR, other nucleic acid amplification techniques have been developed, such as transcription-mediated amplification, loop-mediated isothermal DNA amplification, strand displacement amplification, nucleic acid sequence-based amplification, and branched-chain DNA signal amplification. After amplification, target DNA can be readily detected using a variety of techniques. The amplified product can also be quantified to assess how many microorganisms are present. Quantification of the number of nucleic acids permits serial assessments of response to treatment; the most common clinical application of quantification is the serial measurement of HIV RNA (called viral load).

The direct probe technique, amplified probe technique, and probe with quantification methods vary based on the degree to which the nucleic acid is amplified and the method for measurement of the signal. The direct probe technique refers to detection methods in which nucleic acids are detected without an initial amplification step. The amplified probe technique refers to detection methods in which either target, probe, or signal amplification is used to improve the sensitivity of the assay over direct probe techniques, without quantification of nucleic acid amounts.

- Target amplification methods include PCR (including PCR using specific probes, nested or multiplex PCR), nucleic acid-based sequence amplification, transcription-mediated amplification, and strand displacement amplification. Nucleic acid-based sequence amplification and transcription-mediated amplification involve amplification of an RNA (rather than a DNA) target.
- Probe amplification methods include ligase chain reaction.
- Signal amplification methods include branched DNA (bDNA) probes and hybrid capture methods using an anti-DNA/RNA hybrid antibody.

The probe with quantification techniques refers to quantitative PCR or real-time PCR methods that use a reporter at each stage of the PCR to generate absolute or relative amounts of a known nucleic acid sequence in the original sample. These methods may use DNA-specific dyes (ethidium bromide or SYBR green), hybridization probes (cleavage-based [TaqMan] or displaceable), or primer incorporated probes.

Direct assays will generally have lower sensitivity than amplified probes. In practice, most commercially available probes are amplified, with a few exceptions. For this evidence review, indications for direct and/or amplified probes without quantification are considered together, while indications for a probe with quantification are considered separately.

Classically, identification of microorganisms relies either on the culture of body fluids or tissues or identification of antigens, using a variety of techniques including direct fluorescent antibody technique and qualitative or quantitative immunoassays. These techniques are problematic when the microorganism exists in very small numbers or is technically difficult to culture. Indirect identification of microorganisms by immunoassays for specific antibodies reactive with the microorganism is limited by difficulties in distinguishing between past exposure and current infection.

Potential reasons for a nucleic acid probe to be associated with improved clinical outcomes compared with standard detection techniques include the following (note: in all cases, for there to be clinical utility, making a diagnosis should be associated with changes in clinical management, which could include initiation of effective treatment, discontinuation of other therapies, or avoidance of invasive testing):

- Significantly improved speed and/or efficiency in making a diagnosis.
- Improved likelihood of obtaining any diagnosis in cases where standard culture is difficult. Potential reasons for difficulty in obtaining standard culture include low numbers of the

organisms (e.g., HIV), fastidious or lengthy culture requirements (e.g., *Mycobacteria, Chlamydia*, *Neisseria* species), or difficulty in collecting an appropriate sample (e.g., herpes simplex encephalitis).
- There is no way to definitively make a diagnosis without nucleic acid testing.
- The use of nucleic acid probe testing provides qualitatively different information than that available from standard cultures, such as information regarding disease prognosis or response to treatment. These include cases where quantification of viral load provides prognostic information or is used to measure response to therapy.

The risks of nucleic acid testing include false-positive and false-negative results, inaccurate identification of pathogens by the device, inaccurate interpretation of test results, or incorrect operation of the instrument.
- False-positive results can lead to unnecessary treatment, with its associated toxicities and side effects, including allergic reaction. In addition, true diagnosis and treatment could be delayed or missed altogether.
- False-negative results could delay diagnosis and initiation of proper treatment.
- It is possible that these risks can be mitigated by the use of a panel of selected pathogens indicated by the clinical differential diagnosis while definitive culture results are pending.

Literature Review
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

The evidence review section of this policy update focuses on pathogen panels. The supplemental information section contains supporting information for the medical necessity of the use of the organism-specific nucleic acid amplification tests (NAATs) which have guideline support. Guidelines from the Centers for Disease Control and Prevention, National Institute of Health, Infectious Diseases Society of America, or America Academy of Pediatrics were used to evaluate appropriate indications for the following individual microorganisms: *Bartonella henselae or quintana, Candida* species, *Chlamydia pneumoniae, Chlamydia trachomatis, Clostridium difficile,* cytomegalovirus, enterovirus, hepatitis B virus, hepatitis C virus, herpes simplex virus, human herpesvirus 6, human papillomavirus, HIV-1, influenza virus, *Legionella pneumophila, Mycobacteria* species, *Mycoplasma pneumoniae, Neisseria gonorrhoeae, Staphylococcus aureus, Streptococcus* group A and group B, vancomycin-resistant *Enterococcus,* and Zika virus.

Central Nervous System Bacterial and Viral Panel
Clinical Context and Test Purpose
The purpose of nucleic acid-based central nervous system (CNS) pathogen panels is to provide a diagnostic option that is an alternative to or an improvement on existing tests for individuals with signs and/or symptoms of meningitis and/or encephalitis.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with signs and/or symptoms of meningitis and/or encephalitis.

Interventions
The test being considered is nucleic acid-based CNS pathogen panel.

Testing with a CNS pathogen panel leads to reduced time to diagnosis compared with standard laboratory techniques (approximately 1 to 8 hours).[1]

The FilmArray Meningitis/Encephalitis (ME) Panel (BioFire Diagnostics, Salt Lake City, UT) is a nucleic acid-based test that simultaneously detects multiple bacterial, viral, and yeast nucleic acids from cerebrospinal fluid (CSF) specimens obtained via lumbar puncture from patients with signs and/or symptoms of meningitis and/or encephalitis. The test has been cleared for marketing through the U.S. Food and Drug Administration (FDA) 510(k) process. The test identifies 14 common organisms responsible for community-acquired meningitis or encephalitis:

- Bacteria: *Escherichia coli* K1; *Haemophilus influenzae*; *Listeria monocytogenes*; *Neisseria meningitidis*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*;
- Viruses: Cytomegalovirus; enterovirus; herpes simplex virus 1; herpes simplex virus 2; human herpesvirus 6; human parechovirus; varicella-zoster virus;
- Yeast: *Cryptococcus neoformans/gattii.*

Run-time is approximately 1 hour per specimen.

Comparators
Comparators of interest include culture or serologic tests and CNS pathogen-specific testing (nucleic acid-based testing for individual pathogens).

The standard approach to the diagnosis of meningitis and encephalitis is culture and pathogen-specific polymerase chain reaction (PCR) testing of CSF based on clinical characteristics. These techniques have a slow turnaround time, which can delay administration of effective therapies and lead to unnecessary empirical administration of broad-spectrum antimicrobials.

Outcomes
The general outcomes of interest are test accuracy, test validity, other test performance measures, medication use, symptoms, and change in disease status.

True-positive and true-negative results lead to faster diagnosis and correct treatment, or no unnecessary treatment, as well as fewer repeated tests.

False-positive and false-negative results, inaccurate identification of a pathogen by the testing device, failure to correctly interpret test results, or failure to correctly operate the instrument may lead to misdiagnosis resulting in inappropriate treatment while postponing treatment for the true condition. Such a situation could lead to incorrect, unnecessary, or no treatment, necessity for additional testing, and delay of correct diagnosis and treatment.

Though not completely standardized, follow-up for suspected meningitis and/or encephalitis would typically occur in the days to weeks after a diagnosis decision and initiation of treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- The study population represents the population of interest. Eligibility and selection are described.

- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test, it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., receiver operating characteristic [ROC], area under the receiver operating characteristic curve [AUROC], c-statistic, likelihood ratios) may be included but are less informative.
    - Reported on a validation cohort that was independent of the development cohort.
- Studies should also report reclassification of diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

The systematic review and meta-analysis by Tansarli and Chapin (2019) examined the diagnostic accuracy of the BioFire FilmArray ME panel.[2] Thirteen prospective and retrospective studies conducted from 2016 through 2019 were reviewed (N=3764); 8 were included in the meta-analysis (n=3059). Included in the meta-analysis is the study by Leber et al [2016][3], which is discussed below. Risk of bias among the studies was mixed but tended toward low risk, with the index test aspect being most questionable. No applicability concerns were found in any studies. To be eligible, studies had to provide sensitivity and specificity data compared with a reference standard. Patients in the studies had infections caused by a variety of components found on the panel (bacterial, viral, *Cryptococcus neoformans/gatti*). Table 2 summarizes the sensitivity, specificity, and other measurements of accuracy. The highest proportions of false-positive results were for *Streptococcus pneumoniae* (17.5%) and *Streptococcus agalactiae* (15.4%). The highest proportion of false negatives was seen for herpes simplex virus types 1 and 2, enterovirus, and *C neoformans/gatti*. The rate of false-positive results with the ME panel suggests this method should be used with caution, and additional diagnostic methods should be used to confirm panel results.

Table 2. Accuracy of BioFire FilmArray Meningitis/Encephalitis Panel

Measurement	Sensitivity, Mean %	Specificity, Mean %	PPV, %	NPV, %	False-Positive Results Before and After Adjudication,[a] %		False-Negative Results Before and After Adjudication, %	
					Before	After	Before	After
Value	90.2	97.7	85.1	98.7	11.4	4.0	2.2	1.5
95% CI	86.2 to 93.1	94.6 to 99.0	NR	NR	NR	NR	NR	NR
Range	60 to 100	88 to 100	NR	NR	NR	NR	NR	NR

Source: Tansarli and Chapin (2019)[2]

CI: confidence interval; NPV: negative predictive value; NR: not reported; PPV: positive predictive value.
[a] Adjudication is further investigation of results, which could include further testing, clinician input, or chart review. In this study, it was performed for discordant results between index and reference tests.

The study by Leber et al (2016) was an FDA pivotal study, as well as the largest and 1 of the only prospective studies available.[3] A total of 1560 samples were tested, which were taken from children and adults with available CSF, but not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis (Table 3). Even the most prevalent organisms were present only a small number of times in the samples. The specificities ranged from 98% to 100% and, given the high number of true negatives, the specificities were estimated with tight precision. However, given the small number of true positives, the sensitivities to detect any given organism could not be estimated with precision. A total of 141 pathogens were detected in 136 samples with the FilmArray and 104 pathogens were detected using comparator methods; 43 FilmArray results were false-positive compared with the comparator method and 6 were false-negative. For 21 of the 43 false-positives, repeat testing of the FilmArray, comparator, or additional molecular testing supported the FilmArray results. The remaining 22 false-positives (16% of all positives) were unresolved. Codetections were observed in 3.7% (5/136) of positive specimens. All 5 included a bacterial and viral positive result, and all 5 specimens were found to have a false-positive result demonstrated by comparator testing (Table 4). The investigators suggested that the discrepancies could have been due to specimen contamination or another problem with the assay configuration or testing process.

Smaller studies[4,5] were consistent with Leber (2016) in estimating the specificities for all included pathogens to be greater than 98%. However, there were also a very low number of true-positives for most pathogens in these studies and thus the estimates of sensitivities were imprecise. Relevance, study design, and trial conduct limitations are shown in Tables 5 and 6.

Cuesta et al (2024) prospectively evaluated the performance of a multiplex PCR assay (QIAstat-Dx ME panel) compared to conventional diagnostic methods and the Biofire FilmArray ME Panel for diagnosing meningoencephalitis in 50 CSF samples.[6] Conventional methods identified a pathogen in 29 CSF samples (58%), with 41% bacterial and 59% viral etiologies. The QIAstat-Dx ME panel demonstrated a sensitivity of 96.5% (95% CI, 79.8% to 99.8%) and specificity of 95.2% (95% CI, 75.2% to 99.7%), with high positive predictive values (PPV) and negative predictive values (NPV) (96.4% and 95.2%) and complete agreement (91.8%) with conventional methods based on Cohen's kappa. In contrast, the FilmArray ME panel had a lower sensitivity (85.1%; 95% CI, 55.9% to 90.2%), specificity (57.1%; 95 %CI, 29.6% to 70.3%), positive and negative predictive values and only moderate agreement (43.5%) with conventional methods. The FilmArray ME panel reported 7 single-pathogen and 5 polymicrobial false positive results, most commonly for herpes simplex virus (HSV)-1, while the QIAstat-Dx ME panel had only one false positive (VZV) and one false negative (HSV-1) result. Limitations include the enrichment of positive samples in the QIAstat-Dx ME analysis and the inability to evaluate all panel targets due to a lack of some positive CSF samples.

López et al (2024) retrospectively reviewed the performance of the Biofire FilmArray ME panel compared to conventional diagnostic methods in 313 patients with suspected ME seen at a single-center from 2018 to 2022.[7] FilmArray was positive in 84 cases (26.8%) (HSV-1 [10.9%], varicella zoster virus (VZV) [5.1%], Enterovirus [2.6%], and *S. pneumoniae* [1.9%]). In the 136 cases where both FilmArray and routine methods were performed, there was a 25.7% lack of agreement. In the overall tested population, the sensitivity was estimated to be 81% (95% CI, 70.6% to 89%) with a specificity of 89% (95% CI, 85.4% to 93.4%). The authors reported a high NPV (93.4%; 95 % CI, 89.9% to 95.7%) and modest PPV (73%; 95 %CI, 64.6% to 80.1%). While FilmArray had a low false negative rate of 6.6%, it reported a high false positive rate of 28.6%, mainly due to HSV-1. The authors observed that the PPV dropped to 36.9% in cases without pleocytosis and 70.2% in those lacking high CSF protein levels; other test characteristics were less impacted by individual CSF characteristics. Limitations include the retrospective single-center design and that conventional testing could not be performed on all samples due to insufficient volume.

Table 3. Characteristics of Clinical Validity Studies of Central Nervous System Panel

Author (Year)	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Leber et al (2016)[3]	Children and adults from whom a CSF specimen was available from standard care testing for bacterial culture; not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis.	Nonconcurrent prospective	Culture and PCR	Processed within 7 days of collection or immediately frozen for future testing	Yes
Hanson et al (2016)[5]	Children and adults from whom a CSF specimen was available who	Retrospective, selection	Culture and PCR with discrepancy	Stored up to 2 y after collection	Yes

Author (Year)	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
	had been tested with at least 1 conventional method.	method not clear	resolution LDT PCR		
Graf et al (2017)[4]	Positive samples (children) selected based on positivity of reference method for any of targets on the CNS panel. Negative samples selected based on negativity of reference sample and with preference for samples highly suggestive of meningitis or encephalitis.	Retrospective, convenience	Culture and PCR	Stored up to 2 y after collection	NR

CNS: central nervous system; CSF: cerebrospinal fluid; LDT: laboratory-developed test; NR: not reported; PCR: polymerase chain reaction.

Table 4. Results of Clinical Validity Studies of Central Nervous System Panel

Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% CI)	
					Sensitivity/Positive % Agreement	Specificity/Negative % Agreement
Leber et al (2016)[3]	1643	1560	Insufficient volume, outside the 7-d window, repeat subject, or invalid FilmArray test			
Bacteria						
Escherichia coli K1				0.1	100 (34 to 100)	99.9 (99.6 to 100)
Haemophilus influenzae				0.06	100 (NA)	99.9 (99.6 to 100)
Listeria monocytogenes				0		100 (99.8 to 100)
Neisseria meningitidis				0		100 (99.8 to 100)
Streptococcus agalactiae				0.06	0 (NA)	99.9 (99.6 to 100)
Streptococcus pneumoniae				0.3	100 (51 to 100)	99.2 (98.7 to 99.6)
Viruses						
Cytomegalovirus				0.2	100 (44 to 100)	99.8 (99.4 to 99.9)
Enterovirus				2.9	96 (86 to 99)	99.5 (99.0 to 99.8)
Herpes simplex virus 1				0.1	100 (34 to 100)	99.9 (99.5 to 100)
Herpes simplex virus 2				0.6	100 (72 to 100)	99.9 (99.5 to 100)
Human herpesvirus 6				1.3	86 (65 to 95)	99.7 (99.3 to 99.9)
Human parechovirus				0.6	100 (70 to 100)	99.8 (99.4 to 99.9)
Varicella-zoster virus				0.3	100 (51 to 100)	99.8 (99.4 to 99.9)
Yeast						
Cryptococcus neoformans/Cryptococcus gattii				0.06	100 (NA)	99.7 (99.3 to 99.9)
Hanson et al (2016)[5]	342	342	NR			
Bacteria						
Escherichia coli K1				0.3	100 (3 to 100)	100 (98 to 100)
Haemophilus influenzae				1.5	100 (48 to 100)	100 (97 to 100)
Listeria monocytogenes				0	NA	100 (98 to 100)
Neisseria meningitidis				0.3	100 (3 to 100)	100 (98 to 100)
Streptococcus agalactiae				0.9	67 (9 to 99)	99 (95 to 100)
Streptococcus pneumoniae				1.5	100 (48 to 100)	99 (96 to 100)
Viruses						
Cytomegalovirus				2.0	57 (18 to 90)	100 (91 to 100)

Author (Year)	Initial N	Final N	Excluded Samples	Prevalence of Condition, %	Clinical Validity (95% CI)	
Enterovirus				11.1	97 (86 to 100)	100 (69 to 100)
Herpes simplex virus 1				3.5	93 (66 to 100)	98 (89 to 100)
Herpes simplex virus 2				8.5	100 (88 to 100)	100 (82 to 100)
Human herpesvirus 6				5.6	95 (74 to 100)	100 (93 to 100)
Human parechovirus				0.3	100 (3 to 100)	100 (93 to 100)
Varicella-zoster virus				9.4	100 (89 to 100)	100 (79 to 100)
Yeast						
Cryptococcus neoformans/Cryptococcus gattii				2.6	64 (35 to 87)	NA
Graf et al (2017)[4]	133	133	NR			
Bacteria						
Haemophilus influenzae				NA[a]	100 (1 to 100)[b]	100 (96 to 100)[b]
Streptococcus agalactiae				NA[a]	100 (1 to 100)[b]	100 (96 to 100)[b]
Streptococcus pneumoniae				NA[a]	100 (28 to 100)[b]	100 (96 to 100)[b]
Viruses						
Enterovirus				NA[a]	95 (82 to 99)[b]	100 (94 to 100)[b]
Herpes simplex virus 1				NA[a]	50 (7 to 93)[b]	100 (96 to 100)[b]
Herpes simplex virus 2				NA[a]	100 (1 to 100)[b]	100 (96 to 100)[b]
Human herpes virus 6				NA[a]	100 (9 to 100)[b]	100 (96 to 100)[b]
Human parechovirus				NA[a]	94 (70 to 100)[b]	100 (95 to 100)[b]

CI: confidence interval; CNS: central nervous system; NA: not available; NR: not reported.
[a] Positives and negatives retrospectively selected from a convenience sample with different selection criteria; prevalence is unknown.
[b] Confidence intervals not provided in publication; estimated based on available information.

Tables 5 and 6 display notable limitations identified in each study.

Table 5. Study Relevance Limitations of Studies of Central Nervous System Panels

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Leber et al (2016)[3]	4. Participants not limited to those with high pretest probability for an infectious cause for meningitis or encephalitis.	3. Used investigational version of test but varies from marketed version only in that Epstein-Barr virus is not available in the marketed version.			
Hanson et al (2016)[5]	3. Selection criteria with respect to clinical characteristics not described.	3. Used investigational version (see above).			
Graf et al (2017)[4]	4. Selection criteria varied for positive and negative samples.				

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values) ; 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 6. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Leber et al (2016)[3]			2. Many tests performed on frozen samples.			
Hanson et al (2016)[5]	1. Not clear if participants were consecutive.		2. Many tests performed on frozen samples.		1. Not clear if there were indeterminate samples.	
Graf et al (2017)[4]	2. Selection not random or consecutive and varied for positive and negatives.	1. Not clear if blinded.	2. Many tests performed on frozen samples.		1. Not clear if there were indeterminate samples.	1. Confidence intervals not provided.

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs were available that evaluated clinical utility.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Central Nervous System Bacterial and Viral Panel

The FilmArray ME Panel provides fast diagnoses compared with standard culture and pathogen-specific PCR, and because it combines multiple individual nucleic acid tests, clinicians can test for several potential pathogens simultaneously. The test uses only a small amount of CSF, leaving remaining fluid for additional testing if needed. The test is highly specific for the included organisms. However, due to the low prevalence of these pathogens overall, the sensitivity for each pathogen is not well-characterized. More than 15% of positives in the largest study were reported to be false-positives, which could cause harm if used to make clinical decisions. Also, a negative panel result does not exclude infection due to pathogens not included in the panel.

Gastrointestinal Pathogen Panel

Clinical Context and Test Purpose

The purpose of nucleic acid-based gastrointestinal (GI) pathogen panels is to provide a diagnostic option that is an alternative to or an improvement on existing tests in individuals with signs and/or symptoms of gastroenteritis.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with signs and/or symptoms of gastroenteritis.

The most common 2 types of GI pathogens are either bacterial or viral, including but not limited to the following[8,9,10]:

- Bacterial (common to U.S. and may be foodborne): *Bacillus cereus, Campylobacter, Clostridioides (Clostridium) difficile, Clostridium botulinum, Clostridium perfringens, Cronobacter sakazakii, Esherichia coli, Listeria monocytogenes, Salmonella* spp., *Shigella* spp., *Staphylococcus aureus*, *Yersinia enterocolitica.*
- Viral: norovirus, rotavirus, adenovirus, astrovirus, sapovirus.

Norovirus is the most common cause of foodborne illness in the U.S.[11]

Interventions

The intervention being considered is testing with a nucleic acid-based GI pathogen panel.

These panels are capable of qualitatively detecting the DNA or RNA of multiple pathogens, including but not limited to *Campylobacter*, *Clostridioides (Clostridium) difficile, Plesiomonas shigelloides, Salmonella* spp., *Yersinia* spp., enteroaggregative *Escherichia coli*, enteropathogenic *E coli*, enterotoxigenic *E coli* (ETEC), Shiga toxin-producing *E coli* (STEC)*, E coli* O157, Shigella/ enteroinvasivev*E coli,* adenovirus F 40/41, astrovirus, norovirus, rotavirus, and sapovirus.

For community-acquired diarrheal illness, extensive GI panels for parasites and viruses may be unnecessary because these illnesses are usually self-limited and, as viruses, are treated with supportive care and hydration.[12] In situations in which the GI condition is likely foodborne based on patient history, GI pathogen panels may be limited to the most common pathogens typically found with foodborne illness. For patients who are immune competent, such a panel could include *Salmonella, Campylobacter, Shigella, Cryptosporidium* (parasite), STEC, and *E coli* O157. More pathogen targets may be included if testing for *C difficile* or testing patients who are critically ill or immunocompromised.[12]

Time to a result of testing with a pathogen panel is reduced compared with standard laboratory techniques (<6 hours).[13]

Comparators

Comparators of interest include culture or serologic tests and GI pathogen-specific testing (nucleic acid-based testing for individual pathogens).

Outcomes

The general outcomes of interest are test accuracy, test validity, other test performance measures, medication use, symptoms, and change in disease status.

True-positive and true-negative results lead to faster diagnosis and correct treatment, or no unnecessary treatment, as well as fewer repeated tests.

False-positive and false-negative results, inaccurate identification of a pathogen by the testing device, failure to correctly interpret test results, or failure to correctly operate the instrument may lead to misdiagnosis resulting in inappropriate treatment while postponing treatment for the true condition. Such a situation could lead to incorrect, unnecessary, or no treatment, subsequent testing, and delay of correct diagnosis and treatment.[14]

Though not completely standardized, follow-up for suspected gastroenteritis or GI conditions would typically occur in the weeks to months after a diagnosis decision and initiation of treatment.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test, it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
    - Reported on a validation cohort that was independent of the development cohort.
- Studies should also report reclassification of diagnostic or risk category.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Infectious gastroenteritis may be caused by a broad spectrum of pathogens resulting in the primary symptom of diarrhea. Panels for GI pathogens use multiplex amplified probe techniques and multiplex reverse transcription for the simultaneous detection of many GI pathogens such as *C difficile*, *E coli*, *Salmonella*, *Shigella*, norovirus, rotavirus, and *Giardia*. The performance study of the first FDA-cleared GI panel (xTAG Pathogen Panel [GPP], Luminex Molecular Diagnostics, Inc, Toronto, Ontario, CA), showed high sensitivity and specificity and overall strong positive percent agreement for the organisms on the panel (Table 7).[15]

Table 7. Prospective Performance Data by Organism

Organism	Sensitivity, %	95% CI, %	Specificity, %	95% CI, %
Campylobacter	100	43.8 to 100	98.2	97.3 to 98.8
Cryptosporidium	9.23	66.7 to 98.6	95.5	94.2 to 96.6
E coli O157	100	34.2 to 100	99.2	98.5 to 99.6
Giardia	100	51.0 to 100	96.7	95.5 to 97.6
Salmonella	100	72.2 to 100	98.4	97.6 to 99.0
STEC	100	20.7 to 100	98.6	97.8 to 99.2
Shigella	100	34.2 to 100	98.5	97.7 to 99.1
Organism	**Positive Percent Agreement**	**95% CI, %**	**Negative Percent Agreement**	**95% CI, %**
C. difficile Toxin A/B	93.9	87.9 to 97.0	89.8	87.8 to 91.5
ETEC	25.0	7.1 to 59.1	99.7	99.1 to 99.9
Norovirus GI/GII	94.9	87.5 to 98.0	91.4	89.6 to 92.9
Rotavirus A	100	34.2 to 100	99.8	99.4 to 100

Source: FDA Decision Summary.[15]
CI: Confidence interval; ETEC: enterotoxigenic *Escherichia coli;* STEC: Shiga toxin–producing *E coli.*

Several studies of GI pathogen panels have demonstrated overall high sensitivities and specificities and indicated the panels might be useful for detecting causative agents for GI infections, including both foodborne and infectious pathogens. Claas et al (2013) assessed the performance characteristics of the xTAG Pathogen Panel (GPP; Luminex, Toronto, ON, Canada) compared with traditional diagnostic methods (i.e., culture, microscopy, enzyme immunoassay/direct fluorescent antibody, real-time PCR, or sequencing) using 901 stool samples from multiple sites.[16] The sensitivity of GPP against real-time PCR was >90% for nearly all pathogens tested by real-time PCR; the 1 exception was adenovirus at 20%, but sensitivity could be higher because real-time PCR did not distinguish between adenovirus species. Kahre et al (2014) found similar results when they compared the FilmArray GI panel (BioFire Diagnostics, Salt Lake City, UT, USA) with the xT AG GPP.[17] Both panels detected more pathogens than routine testing. Of 230 prospectively collected samples, routine testing identified 1 or more GI pathogens in 19 (8.3%) samples; FilmArray detected 76 (33.0%), and xT AG detected 69 (30.3%). Two of the most commonly detected pathogens in both assays were *C difficile* (12.6% to 13.9% prevalence) and norovirus (5.7% to 13.9% prevalence). Both panels showed >90% sensitivity for the majority of targets.

Using the xTAG GPP, Beckmann et al (2014) evaluated 296 patients who were either children with gastroenteritis (n=120) or patients who had been to the tropics and had suspected parasite infestation (adults, n=151; children, n=25).[13] Compared with conventional diagnostics, the GPP showed 100% sensitivity for rotavirus, adenovirus, norovirus, *C difficile, Salmonella* species, *Cryptosporidium,* and *Giardia lamblia.* Specificity was >90% for all but norovirus (42%) and *G lamblia* (56%); both also had lower PPV at 46% and 33%, respectively. *Salmonella* species also had low PPV at 43%; all others had 100% PPV. Negative predictive value was 100% for all pathogens.

Buchan et al (2013) evaluated a multiplex real-time PCR assay (ProGastro SSCS, Gen-Probe Prodesse, San Diego, CA) limited to *Campylobacter* spp., *Salmonella* spp., and *Shigella* spp. against culture; and they tested for STEC against broth enrichment followed by enzyme immunoassay.[18] A total of 1244 specimens from 4 U.S. clinical laboratories were tested. Bidirectional sequencing was used to resolve discrepancies between ProGastro and culture or enzyme immunoassay. The overall prevalence of pathogens detected by culture was 5.6%, whereas the ProGastro assay and bidirectional sequencing showed an overall prevalence of 8.3%. The ProGastro SSCS assay showed a sensitivity of 100% and a specificity of 99.4% to 100% for all pathogens. This is compared with a sensitivity of 52.9% to 76.9% and a specificity of 99.9% to 100% for culture compared with ProGastro SSCS assay.

Al-Talib et al (2014) assessed the diagnostic accuracy of a pentaplex PCR assay with specific primers to detect hemorrhagic bacteria from stool samples.[19] The primers, which were mixed in a single reaction tube, were designed to detect *Salmonella* spp., *Shigella* spp., enterohemorrhagic *E. coli*, and *Campylobacter* spp., all of which are a particular danger to children in developing countries. The investigators used 223 stool specimens from healthy children and spiked them with hemorrhagic bacteria. All primers designed had 100% sensitivity, specificity, PPV, and NPV.

Jiang et al (2014) developed a reverse transcription and multiplex real-time PCR assay to identify 5 viruses in a single reaction.[20] The viruses included norovirus genogroups I and II; sapovirus genogroups I, II, IV, and V; human rotavirus A; adenovirus serotypes 40 and 41; and human astrovirus. Compared with monoplex real-time PCR, multiplex real-time PCR assay had sensitivity ranging from 75% to 100%; specificity ranged from 99% to 100%.

The health technology assessment and systematic review by Freeman et al (2017) evaluated multiplex texts to identify GI pathogens in people suspected of having infectious gastroenteritis.[21] Tests in the assessment were xTAG® GPP and FilmArray GI Panel. Eligible studies included patients with acute diarrhea, compared multiplex GI pathogen panel tests with standard microbiology tests, and assessed patient, management, and/or test accuracy outcomes. Of the 23 identified studies, none provided an adequate reference standard for comparing the accuracy of GI panels with standard tests, so sensitivity and specificity analyses were not performed. Positive and negative test agreement were analyzed for individual pathogens for the separate panel products and are not detailed in this review. The meta-analysis of 10 studies found high heterogeneity in participants, country of origin, conventional methods used, and pathogens considered. Using conventional methods as the determinant of clinically important disease, the meta-analysis results suggested GI panel testing is reliable and could supplant current microbiological methods. An increase in false positives would result, along with the potential for overdiagnosis and incorrect treatment. However, if GI panel testing is identifying important pathology being missed with conventional methods, the result could be more appropriate treatments. The clinical importance of these findings is unclear, and an assessment of GI panel testing effect on patient management and outcomes, compared with conventional testing, is needed.

Kosai et al (2021) evaluated the Verigene Pathogens Nucleic Acid Test (Luminex Corporation), testing 268 clinical stool samples for bacteria and toxins and 167 samples for viruses.[22] Of these samples, 256 and 160 samples, respectively, (95.5% and 95.8%) had fully concordant results between the Verigene EP test and the reference methods (which were culture for bacteria and toxins and xTAG GPP for viral detection). Overall sensitivity and specificity were 97.0% and 99.3%, respectively. Sensitivity for individual pathogens ranged from 87.5% to 100%, and specificity ranged from 98.7% to 100%. A total of 13 false-positive and 6 false-negative results were reported.

Ahmed et al (2024) evaluated the performance of the BioFire FilmArray GI Panel for diagnosing infectious diarrhea caused by parasitic and bacterial infections in intensive care unit patients in Egypt.[23] The study included 50 stool samples subjected to conventional identification (microscopic examination, stool culture, and bacterial identification) and molecular diagnosis by the FilmArray Panel. For parasitic infections, the sensitivity and specificity of the panel compared to microscopy were 83.3% and 100% for *Cryptosporidium* oocysts and 100% and 92.5% for *Giardia lamblia* cysts, respectively. For bacterial infections, the BioFire FilmArray GI Panel demonstrated 100% sensitivity and specificity for both *E. coli* and *Salmonella* compared to stool culture. The overall agreement between the BioFire FilmArray GI Panel and conventional methods was 98% for *Cryptosporidium*, 94% for *G. lamblia*, and 100% for both *E. coli* and *Salmonella*.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Meltzer et al (2022) conducted a single-center RCT investigating antibiotic use in patients with moderate to severe suspected infectious diarrhea presenting to the emergency department.[24] Patients were randomized to receive multiplex PCR testing with the BioFire FilmArray GI panel (n=38) or standard care (usual testing or no testing; n=36). In the PCR arm, subjects received antibiotics in 87% of bacterial or protozoal diarrheal infections (13/15) compared to 46% (6/13) in the control arm (p=.042). No significant differences were found between groups in follow-up symptoms as assessed on days 2, 7, and 30, or emergency department length of stay. The study was terminated early due to the COVID-19 pandemic and thus was underpowered. Additional limitations include potential antibiotic prescribing at subsequent healthcare visits that was not captured and lack of a standardized reference test for the control arm.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity.

A 9-month, prospective, multi-center study by Cybulski et al (2018) assessed the effect of the BioFire FilmArray GI PCR panel on clinical diagnosis and decision-making. It also compared the diagnostic accuracy for patients with positive results obtained exclusively using the GI panel with results obtained using conventional stool culture[25] (Table 8). Testing on 1887 consecutive fecal samples was performed in parallel using the GI panel and stool culture. The GI panel detected pathogens in significantly more samples than culture; median time from collection to results and collection to initiation of treatment was also significantly less. The use of a GI panel also led to a significant trend toward targeted rather than empirical therapy (r^2=0.65; p=.009 by linear regression). Results of the GI panels resulted in discontinuation of antimicrobials in 8 of 9 STEC, with just 1 example of GI panel results affecting clinical decision-making (other results summarized in Table 9). Limitations of the study include the limit to 2 hospitals within a single healthcare system and certain subgroups that were too small for analysis. In addition, it was unclear how the historic controls were used since the current samples were tested with both a GI panel and culture.

The prospective study by Beal et al (2017) also aimed to assess the clinical impact of the BioFire FilmArray GI panel[26] (Table 8). Stool samples from 241 patients (180 adults and 61 children) were tested with the GI panel and compared with 594 control patients from the previous year who were tested via culture. The most common pathogens detected by the GI panel were enteropathogenic *E. coli* (n=21), norovirus (n=21), rotavirus (n=15), sapovirus (n=9), and *Salmonella* (n=9). The GI panel patients had significantly fewer subsequent infectious stool tests compared with the control group. The GI panel patients also had 0.18 imaging studies per patient compared with 0.39 (p=.0002) in the control group. The GI panel group spent fewer days on antibiotic(s) per patient: 1.73 versus 2.12 in the control group. In addition, average length of time from stool culture collection to discharge was 3.4 days for the GI panel group and 3.9 days for the controls (p=.04) (other results summarized in Table 9). The GI panel improved patient care in several ways: (1) it identified a range of pathogens that might not have been detected by culture, (2) it reduced the need for other diagnostic tests, (3) it resulted in less unnecessary use of antibiotics, and (4) it led to shorter length of hospital stay. Some limitations of the study include not confirming the results in which the GI panel did not agree with standard testing and using a historical cohort as a control group.

Table 8. Summary of Key Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	Test 1	Test 2
Cybulski et al (2018)[25]	Prospective multi-center, parallel design	U.S.	Jan-Sep 2017 (controls from 2016)	Newly admitted inpatients (<3 d) and outpatients aged 0 to 91 y; historical control group was patients with positive stool samples from same laboratory during the same period the previous year (N=1887 specimens).	BioFire FilmArray GI panel (n=1887 specimens)	Stool culture (n=1887)
Beal et al (2017)[26]	Prospective single-center	U.S.	Jun 2016-Jun 2017 (controls from Jun-Dec 2015)	ED or admitted patients with stool samples submitted with an order for culture; historical controls were from a previous period (N=835).	BioFire FilmArray GI Panel (n=241)	Stool culture (n=594)

ED: emergency department; GI: gastrointestinal; U.S.: United States

Table 9. Summary of Key Observational Comparative Study Results

Study	Pathogens Detected, % of specimens	Time to Results	Time From Collection to Treatment	Empirical Initiation of Antimicrobial, %	Overall Positivity Rate, %	No. of Additional Stool Tests
Cybulski et al (2018)[25]		Median	Median			
GI panel	35.3	18 h	26 h	23.5	NR	NR
Culture	6.0	47 h	72 h	40.0	NR	NR
p value	NA	<.0001	<.0001	.015	NR	NR
Beal et al (2017)[26]		Mean				
GI panel	NR	8.94 h	NR	NR	32.8	0.58
Culture	NR	54.75 h	NR	NR	6.7	3.02
95% CI	NA	1.44 to 82.8	NR	NR	NR	2.89 to 3.14
p value	NA	<.0001	NR	NR	NR	.0001

CI: confidence interval; GI: gastrointestinal; NA: not applicable; NR: not reported.

Section Summary: Gastrointestinal Pathogen Panel

Most GI panels combining multiple individual nucleic acid tests provide faster results compared to standard stool culture. Sensitivity and specificity are generally high, but the yield of testing may be affected by the panel composition. Results of comparisons of conventional methods for ova and parasites to nucleic acid tests are limited. Prospective observational studies were available to evaluate the clinical utility of a GI panel, which was shown in faster turnaround times leading to quicker treatment and a trend away from empirical treatment toward targeted therapy. However, both studies were limited by lack of adjudication of discordant results or the use of only a historical control. A small RCT found a higher rate of appropriate antibiotic prescribing in patients managed with a GI panel, but was terminated early and thus underpowered. Access to a rapid method for etiologic diagnosis of GI infections may lead to more effective early treatment and infection control measures. However, in most instances, when there is suspicion for a specific pathogen, individual tests could be ordered or a limited pathogen panel could be used. There may be a subset of patients with an unusual presentation who would warrant testing for a larger panel of pathogens at once, but that subset has not been well defined.

Respiratory Pathogen Panel

Clinical Context and Test Purpose

The purpose of the nucleic acid-based respiratory pathogen panel is to provide a diagnostic option that is an alternative to or an improvement on existing tests in individuals with signs and/or symptoms of respiratory infection.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with signs and/or symptoms of respiratory infections.

The available evidence also notes that respiratory pathogen panels are particularly effective for high-risk individuals.

High-risk individuals can include:

- Immunocompromised adult or pediatric patients, such as:
    - Hematopoietic stem cell or solid organ transplant recipients;
    - Individuals receiving high-dose chemotherapy and/or steroids;
- Adults who appear acutely ill with respiratory conditions—particularly in certain settings such as influenza outbreaks;
- Critically ill adult individuals—particularly intensive care unit (ICU) patients.

Interventions
The test being considered is the nucleic acid-based respiratory pathogen panel.

The respiratory pathogen panel is used to diagnosis respiratory infection due to bacteria or viruses and to help guide management of the infection. This panel is performed primarily when a patient is seriously ill, hospitalized, and/or at an increased risk for severe infection with complications or multiple infections. Not everyone with symptoms is tested (e.g., fever, aches, sore throat, and cough). Samples are collected by nasopharyngeal swab in universal transport medium or respiratory wash (i.e., nasal wash, nasal aspirate, or bronchoalveolar lavage wash). Examples of these pathogens include adenovirus, coronavirus (HKU1, NL63, 229E, OC43), human metapneumovirus, human rhinovirus/enterovirus, influenza A (H1, H1-2009, H3), influenza B, parainfluenza (1, 2, 3, 4), respiratory syncytial virus, *Bordetella pertussis, Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*.

Comparators
Comparators of interest include culture or serologic tests and respiratory pathogen-specific testing (nucleic acid-based testing for individual pathogens).

Outcomes
The general outcomes of interest are test accuracy, test validity, other test performance measures, medication use, symptoms, and change in disease status.

True-positive and true-negative results lead to faster diagnosis and correct treatment, or no unnecessary treatment, as well as fewer repeated tests.

False-positive and false-negative results, inaccurate identification of a pathogen by the testing device, failure to correctly interpret test results, or failure to correctly operate the instrument may lead to misdiagnosis resulting in inappropriate treatment while postponing treatment for the true condition. Such a situation could lead to incorrect, unnecessary, or no treatment, subsequent testing, and delay of correct diagnosis and treatment.

Follow-up typically occurs in the days and weeks after diagnosis decision and initiation of treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test, it should also be compared with that test.
- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (e.g., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
    - Reported on a validation cohort that was independent of the development cohort.
- Studies should also report reclassification of diagnostic or risk category.

The RCT conducted by Darie et al (2022) was excluded as the Unyvero Hospitalized Pneumonia panel is not currently commercially available in the United States.[27]

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Clark et al (2023) conducted a systematic review and meta-analysis of the impact of multiplex PCR testing among individuals with a suspected acute respiratory tract infection in the hospital setting.[28] Twenty-seven studies representing 17,321 patients were identified for analysis. Multiplex testing was associated with a reduction in both time to results (-24.22 h; 95% CI, -28.70 to -19.74 h) and hospital length of stay (-0.82 days; 95% CI, -1.52 to -0.11). Antivirals were more likely to be prescribed among influenza positive individuals (risk ratio [RR], 1.25; 95% CI, 1.06 to 1.48) as was use of an appropriate infection control facility (RR, 1.55; 95% CI, 1.16 to 2.07).

Huang et al (2018) published a systematic review and meta-analysis of a multiplex PCR system for the rapid diagnosis of respiratory virus infections.[29] Authors summarized diagnostic accuracy evidence on the detection of viral respiratory infections for BioFire FilmArray RP (Film Array), Nanosphere Verigene RV+ test, and Hologic Gen-Probe Prodesse assays. The study reviewed 20 studies with 5510 patient samples. Multiplex PCRs were found to have high diagnostic accuracy with AUROC $\geq$0.98 for all reviewed viruses except adenovirus (AUROC 0.89). All 3 reviewed multiplex PCR systems were shown to be highly accurate.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Several studies of various respiratory viral panels have demonstrated that the multiplex assay detected clinically important viral infections in a single genomic test; thus, may be useful for detecting causative agents for respiratory tract disorders.[30,31,32]

Randomized Controlled Trials

Markussen et al (2024) conducted a prospective, single-center, RCT to evaluate the impact of rapid syndromic PCR testing on pathogen-directed antibiotic treatment in adults presenting to the emergency department with suspected community-acquired pneumonia in Norway.[33] A total of 374 patients were randomized 1:1 to receive either standard care alone or standard care plus BioFire FilmArray Pneumonia plus Panel testing. At 48 hours, significantly more patients in the PCR group received pathogen-directed treatment (35.3% vs 13.4%; OR 3.53; 95% CI, 2.13 to 6.02; p<.001), with a median 9.4-hour faster time to treatment (HR 3.08; 95% CI, 1.95 to 4.89; p<.001). Among the subset with confirmed CAP, these differences were even more pronounced (47.4% vs 15.5% received pathogen-directed treatment; OR 4.90; p<.001). No significant differences were observed in hospital length of stay, 30- or 90-day mortality, or readmission.

Cartuliares et al (2023) conducted a prospective, multicenter, randomized controlled trial to evaluate the impact of point-of-care multiplex PCR on antibiotic prescribing for patients admitted with suspected community-acquired pneumonia in Denmark.[34] Lower respiratory tract samples were collected from 294 patients randomized to either the PCR group (Biofire FilmArray Pneumonia Panel plus added to standard care) or the standard care only group. The primary outcome, prescription of no or narrow-spectrum antibiotics at 4 hours, did not differ significantly between the PCR (62.8%) and standard of care (59.6%) groups (OR, 1.13; 95% CI, 0.96 to 1.34; p=.134). However, the PCR group had significantly more targeted antibiotic prescriptions at 4 hours (OR, 5.68; 95% CI, 2.49 to 12.94; p<.001) and 48 hours (OR, 4.20; 95% CI, 1.87 to 9.40; p<.001), and more adequate prescriptions at 48 hours (OR, 2.11; 95% CI, 1.23 to 3.61; p=.006) and day 5 (OR, 1.40; 95% CI 1.18 to 1.66; p<.001). There were no significant differences in ICU admissions, 30-day readmissions, length of stay, 30-day mortality, or in-hospital mortality.

Andrews et al (2017) published a quasi-randomized study assessing the impact of multiplex PCR on length of stay and turnaround time compared with routine, laboratory-based testing in the treatment of patients aged ≥16 years presenting with influenza-like illness or upper or lower respiratory tract infection (Table 10).[35] Patients were selected at inpatient and outpatient clinics in 3 areas of a hospital. FilmArray RP PCR systems were used. Of eligible patients (N=606), 545 (89.9%) were divided into a control arm (n=211) and an intervention arm (n=334). While PCR testing was not associated with a reduction in length of stay, turnaround time was reduced (see Table 11 for detailed results). Limitations of the study included design and patient allocation (patients were allocated to the intervention arm on even days). Additionally, the patients considered in the study were not noted to be high-risk individuals as defined above, only those with pertinent symptoms.

The parallel-group, open-label RCT by Brendish et al (2017) evaluated the routine use of molecular point-of-care testing (POCT) for respiratory viruses in adults presenting to a hospital with acute respiratory illness (Table 10).[36] In a large U.K. hospital, over 2 winter seasons, investigators enrolled adults within 24 hours of presenting to the emergency department or acute medical unit with acute respiratory illness or fever >37.5°C, or both. A total of 720 patients were randomized (1:1) to either molecular POCT for respiratory viruses (FilmArray Respiratory Panel; n=362) or routine care (n=358), which included diagnosis based on clinical judgment and testing by laboratory PCR at the clinical team's discretion. All patients in the POCT group were tested for respiratory viruses; 158 (45%) of 354 patients in the control group were tested. Because patients presenting with symptoms are often put on antibiotics before tests can be run, the results of the POCTs were unable to influence the outcome in many patients; therefore, a subgroup analysis was necessary for those who were only given antibiotics after test results were available. The results of the analysis showed antibiotics were prescribed for 61 (51%) of 120 patients in the POCT group and for 107 (64%) of 167 in the control group (difference, -13.2%; 95% confidence interval [CI], -24.8% to -1.7%; p=.0289). Mean test turnaround time for POCT was 2.3 hours (standard deviation [SD], 1.4) versus 37.1 hours (SD, 21.5) in the control group. The percentage of patients prescribed a neuraminidase inhibitor who tested positive for influenza was significantly higher for the POCT group than the control group (82% vs. 47%), and it was significantly lower for the percentage who tested negative for influenza (18% vs. 53%). In addition, the time to first dose was 8.8 hours (SD, 15.3) for POCT and 21.0 hours (SD, 28.7) for the control group (see Table 11 for more results). Blinding of the clinical teams to which group a patient had been randomized to was not possible because the purpose of the study was to inform the clinical team of POCT results. In addition, the limit of the study to the winter months means the findings cannot be extrapolated to the rest of the year.

Table 10. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Andrews et al (2017)[a,35]	United Kingdom	1	Jan-Jul 2015	Patients with influenza-like illness/upper RTI +/- lower RTI N=454	FilmArray POCT (even days of month) n=334	Routine, laboratory-based respiratory panel PCR testing +/- atypical serology (odd days) n=211
Brendish et al (2017)[36]	United Kingdom	1	Jan 2015-Apr 2016 and Oct 2015-Apr 2016[b]	Adults who could be recruited within 24 h of triage in ED or arrival at acute medical unit with acute respiratory illness or fever >37.5°C for ≤7 d N=720	FilmArray POCT n=362	Diagnosis based on clinical judgment and PCR testing at clinical team's discretion n=358

ED: emergency department; PCR: polymerase chain reaction; POCT: point of care testing (using FilmArray Respiratory Panel); RCT: randomized controlled trial; RTI: respiratory tract infection.
[a] Quasi-randomized study.
[b] The dates do not make sense because they overlap, likely due to an error in the article. Another place in the article says the "winter seasons in 2014-15 and 2015-16."

Table 11. Summary of Key RCT Results

Study	Test Efficacy	Length of Stay	Antimicrobic Use Duration	All-Cause Mortality[a]	Readmission[b]
Andrews et al (2017)[35]		Median (IQR)	Median (IQR)		
Active	24%	98.6 h (48.1 to 218.4)	6.0 d (4.0 to 7.0)	4%	19%
Comparator	20%	79.6 h (41.9 to 188.9)	6.8 d (5.0 to 7.3)	4%	20%
Estimated intervention effect	NR	NR	Absolute difference in natural logarithm of duration: -0.08 (95% CI, -0.22 to 0.054)	OR: 0.9 (95% CI, 0.3 to 2.2)	OR: 0.9 (95% CI, 0.6 to 1.4)
Adjusted p value	NR	NR	.23	.79	.70
Brendish et al (2017)[36]		Mean (SD)	Mean (SD)		
Active	NR	5.7 d (6.3)	7.2 d (5.1)	3%	13%
Comparator	NR	6.8 d (7.7)	7.7 d (4.9)	5%	16%
Difference (95% CI)	NR	-1.1 d (-2.2 to -0.3)	-0.4 (-1.2 to 0.4)[c]	-2.0% (-4.7% to 0.6%)	-3.0% (-8.3% to 2.0%)
OR (95% CI)	NR	NR	0.95 (0.85 to 1.05)[d]	0.54 (0.3 to 1.2)	0.78 (0.5 to 1.2)
p value	NR	.04	.32	.15	.28

CI: confidence interval; IQR: interquartile range; NR: not reported; OR: odds ratio; RCT: randomized controlled trial; SD: standard deviation.
[a] 30 days post-enrollment.
[b] Within 30 days of study participation.
[c] Mean risk difference.
[d] Unadjusted odds ratio.

Tables 12 and 13 display notable limitations identified in each study.

Table 12. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Andrews et al (2017)[35]	2. Patients allocated to study arms based on even vs. odd days of the week; patient groups unbalanced in favor of FilmArray group.					
Brendish et al (2017)[36]		1. Patients and data collectors not blinded.				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported.

Table 13. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Andrews et al (2017)[35]	4. Patients were not noted to be high-risk				
Brendish et al (2017)[36]				3. Sensitivity and specificity not reported (study was on clinical utility)	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true-positives, true-negatives, false-positives, false-negatives cannot be determined).

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Respiratory Pathogen Panels
The evidence for the clinical validity or clinical utility of respiratory pathogen panels in diagnosing respiratory infections includes systematic reviews, 2 RCTs, and a quasi-randomized study. The systematic review reported that all 3 reviewed multiplex PCR systems were highly accurate. The clinical utility demonstrated by the RCTs showed benefits in test results turnaround time, time to receive treatment, targeted antibiotic prescriptions, and length of hospital stay. Significant differences were not seen in readmission, or mortality.

Large Multiplex Respiratory Panels
Testing for viruses can be done using single-target tests (singleplex), limited multiplex panels with 3 to 5 pathogen targets, or large multiplex panels with 6 or more pathogen targets.

Limited multiplex panels are commercially available for viruses like SARS-CoV-2, influenza A and B, and RSV, and they are practical because they can be conducted in a single reaction through use of different fluorophores for each viral target, reducing reagent and labor costs.[60]

On the other hand, expanded multiplex syndromic panels, which target more than 5 pathogens, including viruses and atypical bacteria, often use advanced technologies such as microfluidics, microelectronics, or labeled beads to achieve high-level multiplexing, but come with higher reagent costs. These panels may distinguish between viral subtypes but are often not cost-effective for most adult outpatients.[60]

Singleplex or limited multiplex panels are ideal for most adult outpatients with respiratory symptoms due to their cost-effectiveness. Stand-alone PCR assays generally perform better for influenza and RSV compared to expanded panels, even though the sensitivity of multiplex panels can range from 80% to over 99%.[60]

Large multiplex panels may provide non-clinically actionable results, adding peace of mind for patients and providers, but come at a high cost, ranging from hundreds to thousands of dollars.[60] Therefore, expanded multiplex panels are often unnecessary for routine testing.

A study by Baghdadi et al. found that after the onset of the COVID-19 pandemic, the clinical use of multiplex NAAT respiratory panels transitioned from primarily using large panels that targeted 12 or more pathogens to favoring smaller panels that targeted 5 or fewer pathogens. This suggests that the shift is likely influenced by several factors, including the availability and cost of testing resources, the low positivity rates of less common pathogens, and the higher clinical utility of smaller respiratory panels that focus on key pathogenic viruses instead of a broad spectrum of pathogens.[61]

Infectious Disease Society of America (IDSA)

Not all molecular studies have reported demonstrable improvements in outcomes or cost savings. This lack of clarity stems from the heterogeneity and variable quality of published studies. Small sample sizes and comparisons to historical controls are common weaknesses of the respiratory diagnostic literature. Furthermore, complexities in results interpretation combined with variable infrastructure to provide results in a timely manner are real-life challenges.[62]

Urogenital Pathogen Panel[61]

Multiplex molecular panels for urinary tract infections (UTIs) are being marketed for rapid detection of multiple organisms and antimicrobial resistance genes. These tests use nucleic acid amplification techniques (e.g., PCR, sequencing) to identify pathogens directly from urine samples. Unlike conventional urine culture, these panels detect a broader range of organisms, including those not typically considered clinically significant.

Literature Review

Fitzpatrick and Morgan (2024) emphasizes that most rapid multiplex molecular panels for other infections (bloodstream, respiratory, CNS) underwent rigorous scientific evaluation and FDA approval. In contrast, urine multiplex molecular tests **lack FDA approval**, standardized protocols, and robust clinical evidence. Existing studies are small, methodologically flawed, and often funded by companies selling these tests, introducing bias. No high-quality trials demonstrate improved diagnostic accuracy or patient outcomes compared to standard urine culture.

Populations

Current utilization is highest among **nursing home residents** and older adults, populations already vulnerable to overtreatment and antibiotic-related harm. The retrospective cohort study cited analyzed Medicare beneficiaries (over 30 million annually) and found a disproportionate increase in testing among these groups.

Interventions

The intervention is the use of **multiplex molecular nucleic acid panels** for diagnosing UTIs. These tests claim to improve detection by identifying multiple organisms and resistance genes in a single assay.

Comparators

The standard comparator is **urine culture**, which remains the gold standard for UTI diagnosis. Urine culture is FDA-approved, widely validated, and significantly less expensive ($8 vs. $585 median per claim).

Outcomes

Desired outcomes include improved diagnostic accuracy, better clinical decision-making, reduced antibiotic misuse, and improved patient health. However, the article from Fitzpatrick and Morgan (2024) reports:

- **No evidence of improved clinical outcomes** with molecular panels.
- Increased risk of **false positives** and misdiagnosis (e.g., asymptomatic bacteriuria).
- Potential for **antibiotic overuse**, leading to resistance, adverse effects, and higher costs.
- Financial harm: $269 million in Medicare spending in 2023 for non-FDA-approved tests.

Direct Evidence

Two small observational studies suggested modest benefits, but both had significant limitations:

- Small sample sizes.
- High risk of bias (one study funded by a test manufacturer).
- No randomized controlled trials. Additionally, one study found **95% positivity in healthy, asymptomatic adults**, indicating poor specificity and clinical relevance.

Review of Evidence

The evidence base is insufficient to support clinical utility:

- **No rigorous trials** demonstrating benefit over urine culture.
- **High risk of harm**: misdiagnosis, unnecessary antibiotics, increased resistance, and financial toxicity.
- **Lack of regulatory oversight**: tests are not FDA-approved and lack standardized protocols.
- **Profit-driven adoption** without proven patient benefit.

Conclusion: Nucleic acid multiplex molecular panels for urogenital pathogens should be considered **investigational** due to the absence of high-quality evidence, lack of FDA approval, and potential for patient harm and increased costs.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Numerous guidelines have been identified concerning the use of nucleic acid amplification tests (NAATs) for the diagnosis of the pathogens discussed in this review. Table 14 provides an index of NAAT recommendation by virus/ infection.

Table 14. Index of NAAT Recommendations by Virus/Infection

Microorganism	Guidelines Recommending the Use of NAATs (Location)	Guidelines Not Recommending the Use of NAATs[a] (Location)
Bartonella hensalae	NIH (2.1.1), IDSA (3.1), AAP (5.1)	NA
Candida species	AAP (5.1), CDC (1.5.1)[b]	IDSA (3.1, 3. 6)
CNS pathogen panel	IDSA (3.2, 3.3)	NA
Chlamydia pneumoniae	AAP (5.1), CDC (1.5.3), IDSA (3.1[c])	NA
Chlamydia trachomatis	CDC (1.5.2,[c] 1.6[c]), IDSA (3.1), AAP (5.1)	NA
Clostridioides (Clostridium) difficile	NIH (2.1.2, AAP (5.1)	IDSA (3.1, 3.4)
Cytomegalovirus	CDC (1.1), NIH (2.1.3), IDSA (3.1,[c] 3.3)	AAP (5.1)

Microorganism	Guidelines Recommending the Use of NAATs (Location)	Guidelines Not Recommending the Use of NAATs[a] (Location)
Enterovirus	IDSA (3.1), AAP (5.1)	NA
Gardnerella vaginalis	AAP (5.1), CDC (1.5.4)	IDSA (3.1)
GI pathogen panel	CDC (1.4[c]), IDSA (3.5), ACG (6.1)	NA
Hepatitis B	NIH (2.1.4), IDSA (3.1), AAP (5.1)	NA
Hepatitis C	CDC (1.5.5[c]), NIH (2.1.5), IDSA (3.1), AAP (5.1)	NA
Herpes simplex virus	CDC (1.5.6[c]), NIH (2.1.6), IDSA (3.1,[c] 3.3), AAP (5.1)	NA
Human herpesvirus 6	IDSA (3.1,[c] 3.3)	AAP (5.1)
Human papillomavirus	CDC (1.5.8[c]), AAP (5.1)	NA
HIV 1	CDC (1.5.7[c]), IDSA (3.1), AAP (5.1)	NA
Influenza virus	IDSA (3.1[c]), AAP (5.1)	NA
Legionella pneumophila	IDSA (3.1), AAP (5.1)	NA
Meningitis	NA	IDSA (3.2)
Mycobacteria species	AAP (5.1), CDC (1. 7), NIH (2.1.7), IDSA (3.1, 3.3)	AAP (5.1)
Mycoplasma pneumoniae	CDC (1.2[c]), IDSA (3.3), AAP (5.1)	NA
Neisseria gonorrhoeae	CDC (1.6[c]), IDSA (3.1), AAP (5.1)	NA
Respiratory panel	None Identified	NA
SARS-CoV-2	IDSA (3. 7)	NA
Staphylococcus aureus	IDSA (3.1), AAP (5.1)	NA
Streptococcus, group A	AAP (5.2), IDSA (3.1)	AAP (5.1)
Streptococcus, group B	AAP (5.2), ASM (7.1)	IDSA (3.1), AAP (5.1)
Trichomonas vaginalis	CDC (1.5.9), IDSA (3.1),[c] AAP (5.1)	NA
Vancomycin-resistant *Enterococcus*	AST (4.1)	IDSA (3.1), AAP (5.1)
Zika virus	CDC (1.3), IDSA (3.1), AAP (5.1)	NA

AAP: American Academy of Pediatrics; ACG: American College of Gastroenterology; ASM: American Society for Microbiology; AST: American Society of Transplantation; CDC: Centers for Disease Control and Prevention; CNS: central nervous system; GI: gastrointestinal; HIV: human immunodeficiency virus; IDSA: Infectious Disease Society of America; NA: not applicable (none found); NAAT: nucleic acid amplification test; NIH: National Institutes of Health; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

[a] Guidelines Not Recommending includes not only guidelines that recommend against NAATs but also those that were neutral on the use of NAATs.

[b] CDC recommends culture for first-line identification of *Candida* species; it recommends NAAT for complicated infections and for second-line diagnosis.

[c] Indicates guidelines in which the issuing body specifically recommends that U.S. Food and Drug Administration (FDA)-cleared NAATs be used.

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC) have published multiple recommendations and statements regarding the use of NAATs to diagnose the viruses and infections discussed in this evidence review since 2009.

1.1 The CDC published guidance for laboratory testing for cytomegalovirus (CMV); the guideline stated that the standard laboratory test for congenital CMV is polymerase chain reaction (PCR) on saliva, with confirmation via urine test to avoid false-positive results from ingesting breast milk from CMV seropositive mothers. Serologic tests were recommended for persons >12 months of age.[37]

1.2 The CDC published diagnostic methods for mycoplasma pneumoniae.[38] They cited NAAT as a method of diagnosis, along with culture or serology.

1.3 The CDC published updated guidelines on Zika virus testing.[39] Routine testing for Zika virus in asymptomatic pregnant patients is not recommended, but NAAT testing may still be considered for asymptomatic pregnant women with recent travel to an area with risk of Zika outside the U.S. and its territories. Symptomatic pregnant patients should receive NAAT testing if they have recently traveled to areas with a risk of Zika virus or if they have had sex with someone who lives in or recently traveled to areas with risk of Zika virus. If a pregnant woman (with risk of Zika virus exposure) has a fetus with prenatal ultrasound findings consistent with congenital Zika virus infection, Zika virus NAAT and IgM testing should be performed on maternal serum and NAAT on maternal urine. If amniocentesis is being performed as part of clinical care, Zika virus NAAT testing of amniocentesis specimens should also be performed.

1.4 In 2017, the CDC updated its guidelines on norovirus gastroenteritis outbreak management and disease prevention.[40,41] Real-time reverse transcription-PCR assays, specifically, TaqMan-based real-time assays, which can contain multiple probes, is considered the effective laboratory diagnostic protocol for testing suspected cases of viral gastroenteritis.

1.5 In 2015, the CDC made recommendations for the use in NAATs in diagnosing numerous sexually transmitted infections.[42] These recommendations were most recently updated in 2021, with the publication of new guidelines and the following recommendations:[43]

1.5.1 For *Candida* species:

- "The majority of PCR tests for yeast are not FDA [U.S. Food and Drug Administration] cleared, and providers who use these tests should be familiar with the performance characteristics of the specific test used."

1.5.2 For Gonococcal Infections:

- "Culture, NAAT, and POC [point of care] NAAT, such as GeneXpert (Cepheid), are available for detecting genitourinary infection with *N. gonorrhoeae*."
- "NAATs and POC NAATs allow for the widest variety of FDA-cleared specimen types, including endocervical and vaginal swabs and urine for women, urethral swabs and urine for men, and rectal swabs and pharyngeal swabs for men and women. However, product inserts for each NAAT manufacturer should be consulted carefully because collection methods and specimen types vary."

1.5.3 For Chlamydial Infection:

- "NAATs are the most sensitive tests for these specimens and are the recommended test for detecting *C. trachomatis* infection. NAATs that are FDA cleared for use with vaginal swab specimens can be collected by a clinician or patient in a clinical setting. Patient collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a clinician using NAATs, and this screening strategy is highly acceptable among women. Optimal urogenital specimen types for chlamydia screening by using NAAT include firstcatch urine (for men) and vaginal swabs (for women). Recent studies have demonstrated that among men, NAAT performance on self-collected meatal swabs is comparable to patient-collected urine or provider-collected urethral swabs."

1.5.4 For *Gardnerella vaginalis*:

- "Multiple BV [bacterial vaginosis] NAATs are available for BV diagnosis among symptomatic women. These tests are based on detection of specific bacterial nucleic acids and have high sensitivity and specificity for BV (i.e., *G. vaginalis, A. vaginae*, BVAB2, or Megasphaera type 1) and certain lactobacilli (i.e., *Lactobacillus crispatus, Lactobacillus jensenii*, and *Lactobacillus gasseri*)…Five quantitative multiplex PCR assays are available…Two of these assays are FDA cleared (BD Max Vaginal Panel and Aptima BV), and the other three are laboratory-developed tests."

1.5.5 For hepatitis C infection (HCV):

- In addition, "testing for HCV infection should include use of an FDA-cleared test for antibody to HCV…followed by NAAT to detect HCV RNA for those with a positive antibody result. Persons with HIV infection with low CD4+ T-cell count might require further testing by NAAT because of the potential for a false-negative antibody assay."

1.5.6 For diseases characterized by genital, anal, or perianal ulcers (e.g., herpes simplex virus [HSV], syphilis)

- "Specific evaluation of genital, anal, or perianal ulcers includes syphilis serology tests and darkfield examination from lesion exudate or tissue, or NAAT if available; NAAT or culture for genital herpes type 1 or 2; and serologic testing for type-specific HSV antibody. In settings where chancroid is prevalent, a NAAT or culture for *Haemophilus ducreyi* should be performed;" and
- "PCR is also the test of choice for diagnosing HSV infections affecting the central nervous system (CNS) and systemic infections (e.g., meningitis, encephalitis, and neonatal herpes). HSV PCR of the blood should not be performed to diagnose genital herpes infection, except in cases in which concern exists for disseminated infection (e.g., hepatitis)."

1.5.7 For *Human immunodeficiency virus 1* (HIV-1):

- The use of NAAT is not mentioned; serologic tests are recommended for detecting antibodies against HIV-1 and by virologic tests that detect HIV antigens or RNA.

1.5.8 For human papillomavirus (HPV):

- There are several FDA-cleared HPV tests that detect viral nucleic acid or messenger RNA; however, there are currently no algorithms for HPV 16/18/45 testing in the clinical guidelines;
- Testing for nononcogenic HPV (types 6 and 11) is not recommended; and
- “HPV assays should be FDA-cleared and used only for the appropriate indications” and should not be performed if the patient is “deciding whether to vaccinate against HPV;” when “providing care to persons with genital warts or their partners;” when “testing persons aged <25 years as part of routine cervical cancer screening;” or when “testing oral or anal specimens.”

1.5.9 For *Trichomonas vaginalis*:

- NAAT is recommended for detecting *T vaginalis* in women due to its high sensitivity and specificity. Multiple assays are FDA-cleared to detect *T vaginalis* from vaginal, endocervical, or urine specimens for women.
- Although there is not a currently FDA-cleared assay test available for use in men, assays "...should be internally validated in accordance with CLIA [Clinical Laboratory Improvement Amendments] regulations before use with urine or urethral swabs from men."

1.6 In 2014, the CDC published recommendations regarding the laboratory-based detection of *C. trachomatis* and *N. gonorrhoeae* infections.[44] It stated:

- NAATs are superior other available diagnostic tests in “overall sensitivity, specificity, and ease of specimen transport;”
- The use of “NAAT to detect chlamydia and gonorrhea except in cases of child sexual assault involving boys and rectal and oropharyngeal infections in prepubescent girls” is supported by evidence; and
- Only NAATs that have been cleared by the FDA for detection of *C. trachomatis* and *N. gonorrhoeae* should be used “as screening or diagnostic tests because they have been evaluated in patients with and without symptoms.”

1.7 In 2009, the CDC published updated guidelines for the use of NAATs in diagnosing *Mycobacterium tuberculosis* bacteria.[45] The CDC recommended that “NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB [tuberculosis] for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities.” Although it noted that “culture remains the gold standard for laboratory confirmation of TB and is required for isolating bacteria for drug-susceptibility testing and genotyping,” the guideline stated that “NAA testing should become standard practice for patients suspected to have TB, and all clinicians and public health TB programs should have access to NAA testing for TB to shorten the time needed to diagnose TB from 1 to 2 weeks to 1 to 2 days.”

1.8 In 2021, the CDC published Sexually Transmitted Infections Treatment Guidelines. The CDC recommendations note that: "*M. genitalium* is an extremely slow-growing organism. Culture can take up to 6 months, and technical laboratory capacity is limited to research settings. NAAT for *M. genitalium* is FDA cleared for use with urine and urethral, penile meatal, endocervical, and vaginal swab samples. Molecular tests for macrolide (i.e., azithromycin) or quinolone (i.e., moxifloxacin) resistance markers are not commercially available in the United States. However, molecular assays that incorporate detection of mutations associated with macrolide resistance are under evaluation. Men with recurrent NGU should be tested for *M. genitalium* using an FDA-cleared NAAT. If resistance testing is available, it should be performed and the results used to guide therapy. Women with recurrent cervicitis should be tested for *M. genitalium*, and testing should be considered among women with PID. Testing should be accompanied with resistance testing, if available. Screening of asymptomatic *M. genitalium* infection among women and men or extragenital testing for *M. genitalium* is not recommended. In clinical practice, if testing is unavailable, *M. genitalium* should be suspected in cases of persistent or recurrent urethritis or cervicitis and considered for PID."[46]

National Institutes of Health et al

2.1 The National Institute of Health (NIH), CDC, and HIV Medicine Association of the Infectious Diseases Society of America (IDSA) published guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV.[47] The most recent update took place in 2025. In these guidelines, NAATs are discussed in the following situations:

2.1.1 *Bartonella* species

- For patients with suspected bacillary angiomatosis, serologic tests are the standard of care and the most accessible test for diagnosing Bartonella infection. There are PCR methods that have been developed for identification and speciation of *Bartonella* and are becoming increasingly available through private laboratories, as well as the CDC and may aid in diagnosis of *Bartonella* in freshly biopsied tissue samples or whole blood.

2.1.2 *Clostridioides (Clostridium) difficile*

- Detection of either the *C. difficile* toxin B gene, using NAAT, or the *C. difficile* toxin B protein, using an enzyme immunoassay, is required for diagnosis. PCR assays have high sensitivity and can detect asymptomatic carriers.

2.1.3 Cytomegalovirus

- For patients with suspected CMV disease, diagnosis is based on clinical symptoms and the presence of CMV in cerebral spinal fluid (CSF) or brain tissue. "In rare cases, the diagnosis may be unclear, and PCR of aqueous or vitreous humor specimens for CMV and other pathogens—especially herpes simplex virus, varicella zoster virus, and Toxoplasma gondii—can be useful for establishing the diagnosis."

2.1.4 Hepatitis B

- The CDC, the United States Preventive Services Task Force, and the American Association for the Study of Liver Disease (AASLD) recommend that patients with HIV infection should be tested for hepatitis B; however, NAATs are not recommended for initial testing in patients with HIV.

2.1.5 Hepatitis C

- Patients with HIV are recommended to undergo routine hepatitis C screening, initially "performed using the most sensitive immunoassays licensed for detection of antibody to HCV in blood." The use of NAATs are not mentioned for initial testing in patients with HIV.

2.1.6 Herpes Simplex Virus

- "HSV DNA PCR and viral culture are preferred methods for diagnosis of mucocutaneous lesions potentially caused by HSV."

2.1.7 *Mycobacterium tuberculosis* infection and disease

- " NAA tests provide rapid diagnosis of TB, and some assays also provide rapid detection of drug resistance."

- "NAA assays, if positive, are highly predictive of TB disease when performed on Acid-Fast Bacillus (AFB) smear-positive specimens. However, because nontuberculous mycobacterial infections (NTM) may occur in people with HIV with advanced immunodeficiency, negative NAA results in the setting of smear-positive specimens may indicate NTM infection and can be used to direct therapy and make decisions about the need for respiratory isolation."
- "NAA tests are more sensitive than AFB smear, being positive in 50% to 80% of smear negative, culture-positive specimens and up to 90% when three NAA tests are performed. Therefore, it is recommended that for all patients with suspected pulmonary TB, a NAA test be performed on at least one specimen. NAA tests also can be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than with sputum specimens."

Infectious Disease Society of America et al

Since 2008, the IDSA has partnered with various societies to publish 9 recommendations regarding the use of NAATs to diagnose the viruses and infections discussed in this evidence review.

3.1 In 2024, the IDSA and the American Society for Microbiology published a guide on the diagnosis of infectious diseases.[48] In this guideline, NAATs were recommended diagnostic procedures for enterovirus, hepatitis C, hepatitis B, cytomegalovirus, bacterial vaginosis, herpes simplex virus, human herpesvirus 6, HIV, influenza virus, and Zika virus. In addition to providing guidance on diagnosing these diseases, the guidelines also provided recommendations on testing for other conditions by testing for common etiologic agents. Table 15 describes selected conditions for which IDSA recommends NAATs for diagnosing etiologic agents.

Table 15. IDSA Recommended Conditions for Use of NAATs in Identifying Etiologic Agents of Other Conditions*

Etiologic Agents	Recommended Conditions for Use of NAATs in Diagnosis when Specific Etiologic Agents is Suspected
Bartonella spp	Bloodstream infections; encephalitis
Chlamydia pneumoniae	Bronchiolitis, bronchitis, and pertussis; community- acquired pneumonia
Chlamydia trachomatis	Pre-septal and orbital cellulitis, lacrimal and eyelid infections, and conjunctivitis; pharyngitis; orbital and periorbital cellulitis, and acrimal and eyelid infections; proctitis; epididymitis and orchitis; pathogens associated with cervicitis/ urethritis; pathogens associated with pelvic inflammatory disease and endometritis
Clostridioides (Clostridium) difficile	Gastroenteritis, infectious, and toxin- induced diarrhea
Cytomegalovirus	Pericarditis and myocarditis[a]; encephalitis; pneumonia in the immunocompromised host; esophagitis; gastroenteritis, infectious, and toxin-induced diarrhea; burn wound infections[b]
Enterovirus	Meningitis; encephalitis; brochiolitis, bronchitis, and pertussis; community-acquired pneumonia; gastroenteritis, infectious, and toxin- induced diarrhea; pre-septal and orbital cellulitis, lacrimal and eyelid infections, and conjunctivitis; infectious keratitis; endophthalmitis, panophtalmitis, uveitis, and retinitis
Herpes simplex virus	Meningitis; encephalitis; esophagitis; proctitis; pathogens associated with cervicitis/ urethritis; burn wound infection[b]; periocular structure infections/ conjunctivitis, orbital and periorbital cellulitis, and acrimal and eyelid infections; periocular structure infections/ keratitis; pharyngitis; genital lesions; endophthalmitis, panophthalmitis, uveitis, and retinitis; pneumonia in the immunocompromised host
HIV	Pericarditis and myocarditis; meningitis[c]; pharyngitis[c]
Human herpesvirus 6	Encephalitis
Influenza virus	Encephalitis; bronchiolitis, bronchitis, and pertussis; community- acquired pneumonia; hospital- acquired pneumonia and ventilator- associated pneumonia; pulmonary infections in cystic fibrosis

Etiologic Agents	Recommended Conditions for Use of NAATs in Diagnosis when Specific Etiologic Agents is Suspected
Legionella spp	Community- acquired pneumonia; hospital- acquired pneumonia and ventilator- associated pneumonia; surgical site infections
Mycobacteria species- both tuberculosis and NTM	Community- acquired pneumonia; infections of the pleural space; meningitis; osteomyelitis; encephalitis
Neisseria gonorrhoeae	Joint infection; pharyngitis; proctitis; native joint infection and bursitis; epididymitis and orchitis; pathogens associated with cervicitis/ urethritis; pathogens associated with pelvic inflammatory disease and endometritis
Staphylococcus aureus	Joint infection; trauma-associated cutaneous infection; surgical site infections; osteomyelitis
Streptococcus, group A	Pharyngitis; periprosthetic joint infection
Trichomonas vaginalis	Pathogens associated with cervicitis/ urethritis; pathogens associated with pelvic inflammatory disease and endometritis; epididymitis and orchitis

* The IDSA provided recommendations for many situations in which NAATs are recommended for diagnosing certain etiologic agents commonly seen, with the listed conditions noted under the Recommended Conditions for Use of NAATs in Diagnosis Column.
HIV: human immunodeficiency virus; IDSA: Infectious Disease Society of America; MRSA: methicillin-resistant *Staphylococcus aureus*; NAAT: nucleic acid amplification test: NTM: nontuberculous mycobacteria.
[a] Recommended as first choice if available.
[b] Where applicable and laboratory-validated.
[c] The guidelines caution that NAAT is not 100% sensitive in individuals with established HIV infection due to viral suppression; therefore, if NAAT is used, subsequent serologic testing is recommended.

Use of NAATs for diagnosing *Candida* species, *Gardnerella vaginalis*, *Streptococcus* group B, and vancomycin-resistant *Enterococcus* as etiologic agents was not recommended.

3.2 In 2017, the IDSA published clinical practice guidelines for the management of healthcare-associated ventriculitis and meningitis.[49] When making diagnostic recommendations, the IDSA notes cultures as the standard of care in diagnosing healthcare-associated ventriculitis and meningitis, but that "nucleic acid amplification tests, such as PCR, on CSF may both increase the ability to identify a pathogen and decrease the time to making a specific diagnosis (weak, low)." (Strength of recommendation and quality of evidence established using the GRADE [Grading of Recommendations Assessment, Development and Evaluation] methodology).

3.3 In 2008, the IDSA published clinical practice guidelines for the management of encephalitis.[50] The following recommendations were made:

- The use of NAATs was recommended for diagnosing CMV, herpes simplex virus 1 and 2, human herpesvirus 6, *Bartonella henselae*, *Mycoplasma pneumoniae*, and *Mycobacterium tuberculosis*.

3.4 In 2018, the IDSA and the Society for Healthcare Epidemiology of America (SHEA) published weak recommendations with low quality evidence for the use of NAATs to diagnose *Clostridioides (Clostridium) difficile*.[52]

- "The best-performing method (i.e., in use positive and negative predictive value) for detecting patients at increased risk for clinically significant *C. difficile* [CDI] infection" is use of a "stool toxin test as part of a multistep algorithm...rather than NAAT along for all specimens received in the clinical laboratory when there are no preagreed institutional criteria for patient stool submission."
- "The most sensitive method of diagnosis of CDI in stool specimens from patients likely to have CDI based on clinical symptoms" is use of "a NAAT alone or a multistep algorithm for testing...rather than a toxin test alone when there are preagreed institutional criteria for patient stool submission."

3.5 In 2017, the IDSA published clinical practice guidelines for the diagnosis and management of infectious diarrhea.[53] The following recommendations were made:

- In situations where enteric fever or bacteremia is suspected, "culture-independent, including panel-based multiplex molecular diagnostics from stool and blood specimens, and when indicated, culture-dependent diagnostic testing should be performed" (GRADE: strong, moderate).
- In testing for *Clostridioides (Clostridium) difficile* in patients >2 years of age, "a single diarrheal stool specimen is recommended for detection of toxin or toxigenic C. difficile strain (e.g., nucleic acid amplification testing)" (GRADE: strong, low).
- NAATs are not recommended for diagnosing CMV.
- It was also noted that "clinical consideration should be included in the interpretation of results of multiple-pathogen nucleic acid amplification tests because these assays detect DNA and not necessarily viable organisms" (GRADE: strong, low).

3.6 In 2016, the IDSA published updated clinical practice guidelines for managing candidiasis.[54] The guideline noted many limitations of PCR testing. No formal recommendation was made, but the guidelines did state that "the role of PCR in testing samples other than blood is not established."

3.7 In 2020, the IDSA established a panel composed of 8 members including frontline clinicians, infectious diseases specialists and clinical microbiologists who were members of the IDSA, American Society for Microbiology, SHEA, and the Pediatric Infectious Diseases Society (PIDS). Panel members represented the disciplines of adult and pediatric infectious diseases, medical microbiology, as well as nephrology and gastroenterology. The panel created a coronavirus disease 2019 (COVID-19) diagnosis guideline using the GRADE approach for evidence assessment; and, given the need for rapid response to an urgent public health crisis, the methodological approach was modified according to the GIN/McMaster checklist for development of rapid recommendations. The panel published recommendations for COVID-19 diagnosis in an online format, as when substantive new information becomes available the recommendations will require frequent updating.[55] The current recommendations (published December 23, 2020) support *Severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) nucleic acid testing for the following groups:

- all symptomatic individuals suspected of having COVID-19;
- asymptomatic individuals with known or suspected contact with a COVID-19 case;
- asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a high prevalence of COVID-19 in the community;
- asymptomatic individuals who are immunocompromised and being admitted to the hospital, regardless of COVID-19 exposure;
- asymptomatic individuals prior to hematopoietic stem cell transplant or solid organ transplantation, regardless of COVID-19 exposure;
- asymptomatic individuals without known exposure to COVID-19 undergoing major time-sensitive surgeries;
- asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when personal protective equipment (PPE) is limited, and testing is available;
- asymptomatic individuals without known exposure when the results will impact isolation/quarantine/ PPE usage decisions, dictate eligibility for surgery, or inform administration of immunosuppressive therapy.

The IDSA panel further recommends the following:

- collecting nasopharyngeal swab, mid-turbinate swab, anterior nasal swab, saliva or a combined anterior nasal/oropharyngeal swab rather than oropharyngeal swabs alone for SARS-CoV-2 RNA testing in symptomatic individuals with upper respiratory tract infection or influenza like illness suspected of having COVID-19 (conditional recommendation, very low certainty of evidence).

- nasal and mid-turbinate swab specimens may be collected for SARS-CoV-2 RNA testing by either patients or healthcare providers, in symptomatic individuals with upper respiratory tract infection or influenza like illness suspected of having COVID-19 (conditional recommendation, low certainty of evidence).
- a strategy of initially obtaining an upper respiratory tract sample (e.g., nasopharyngeal swab) rather than a lower respiratory sample for SARS-CoV-2 RNA testing in hospitalized patients with suspected COVID-19 lower respiratory tract infection. If the initial upper respiratory sample result is negative, and the suspicion for disease remains high, the IDSA panel suggests collecting a lower respiratory tract sample (e.g., sputum, bronchoalveolar lavage fluid, tracheal aspirate) rather than collecting another upper respiratory sample (conditional recommendations, very low certainty of evidence).
- performing a single viral RNA test and not repeating testing in symptomatic individuals with a low clinical suspicion of COVID-19 (conditional recommendation, low certainty of evidence).
- repeating viral RNA testing when the initial test is negative (versus performing a single test) in symptomatic individuals with an intermediate or high clinical suspicion of COVID-19 (conditional recommendation, low certainty of evidence).
- using either rapid reverse-transcriptase (RT)-PCR or standard laboratory-based NAATs over rapid isothermal NAATs in symptomatic individuals suspected of having COVID-19 (conditional recommendation, low certainty of evidence).

American Society of Transplantation

4.1 In 2019, the American Society of Transplantation Infectious Diseases Community of Practice published guidelines which addressed vancomycin-resistant enterococci (VRE) infections in solid organ transplant patients.[56] The guidelines noted the cost-effectiveness and accuracy of "emerging molecular diagnostics for VRE colonization, including multiplexed PCR performed after culture on selective media," compared with culture alone.

American Academy of Pediatrics

5.1 The thirty- third edition of the American Academy of Pediatrics (AAP) Red Book (2024) describes the diagnostic and treatment options for many infectious diseases in the pediatric population.[57] Their recommendations for appropriate diagnostic tests for the viruses and infections discussed in this policy are detailed in Table 16.

Table 16. Red Book Diagnostic Test Recommendations for the Pediatric Population

Infection	Diagnostic Test Recommendation
Bartonella henselae	EIA IFA NAAT (PCR)
Candida species	Clinical evaluation microscopy PNA FISH probes and PCR assays developed for rapid detection directly from positive blood culture
Chlamydia pneumoniae	NAATs (PCR) are the preferred method for diagnosis of acute infection Serologic antigen test is an option, but is technically complex and interpretation is subjective
Chlamydia trachomatis	NAATs are recommended for *C trachomatis* urogenital infections and in postpubescent individuals. They are not recommended for diagnosing *C trachomatis* conjunctivitis or pneumonia or in the evaluation of prepubescent children for possible sexual assault.
Clostridioides (Clostridium) difficile	NAATs have become the most common diagnostic test for toxigenic strains of *C difficile* in both adult and pediatric hospitals. NAATs detect genes responsible for the production of toxins A and B, rather than free toxins A and B in the stool, which are detected by EIA

Infection	Diagnostic Test Recommendation
	NAAT could be considered alone if a policy in place to screen symptoms; if no policy in place, multi-step algorithms involving EIA, GDH, NAAT plus toxin is recommended
Coronaviruses (including SARS-CoV-2 and MERS-CoV)	RT-PCR Direct antigen testing
Cytomegalovirus	Saliva PCR is the preferred diagnostic tool for screening.
Enterovirus	RT-PCR and culture from a variety of specimens
Gardnerella vaginalis	Microscopy Numerous NAATs have been recommended when microscopy is unavailable. NAATs should only be used to test symptomatic patients.
Hepatitis B	Serologic antigen tests NAATs
Hepatitis C	IgG antibody enzyme immunoassays NAATs
Herpes simplex virus	Cell culture NAATs
Human herpesvirus 6	Few developed assays are available commercially and do not differentiate between new, past, and reactivated infection. Therefore, these tests "have limited utility in clinical practice:" Serologic tests; PCR
HIV	Serologic tests; NAATs or RNA PCR- preferred test to diagnose HIV infection in infants and children younger than 18mo;
Human papillomavirus	NAATs - increasingly favored for female individuals starting at age 25 years
Influenza virus	NAATs, immunofluorescence assays, rapid influenza diagnostic tests, rapid cell culture, and viral tissue cell culture are available options for testing; optimal choice of influenza test depends on the clinical setting.
Legionella pneumophila	BCYE media Legionella antigen in urine Direct IFA Genus and species specific NAATr assays
Meningitis	Cultures of blood and CSF NAATs- "useful in patients who receive antimicrobial therapy before cultures are obtained."
Mycobacteria species	*M tuberculosis* disease: Chest radiography and physical examination Isolation of *M tuberculosis* complex by culture from a specimen of sputum, gastric aspirate, nasopharyngeal aspirate, bronchial washing, pleural fluid, cerebrospinal fluid, urine or other body fluid, or a tissue biopsy specimen NAATs - "Culture isolation of the organism is still required for phenotypical susceptibility testing, genotyping, most rapid molecular detection of drug-resistance genes, and species identification. Expert consultation is recommended for test availability and interpretation of results"
Mycoplasma pneumoniae	NAATs - NAATs for *M pneumoniae* are available commercially and increasing replacing other tests, because PCR tests performed on respiratory tract specimens have sensitivity and specifically between 80% and 100%, yield positive results earlier in the course of illness than serologic tests, and are rapid.
Neisseria gonorrhoeae	"NAATs are far superior in overall performance compared with other *N gonorrhoeae* culture and nonculture diagnostic methods to test genital and nongenital specimens"

Infection	Diagnostic Test Recommendation
Staphylococcus aureus	NAATS are approved for detection and identification of *S aureus*, including MRSA, in positive blood cultures.
Streptococcus, group A	"Children with pharyngitis and obvious viral symptoms should not be tested or treated for group A streptococcal infection...Laboratory confirmation before initiation of antimicrobial treatment is required for cases in children without viral symptoms... culture on sheep blood agar can confirm group A streptococcal infection." "The US Food and Drug Administration has approved some NAATs for detection of group A streptococci from throat swab specimens as stand-alone tests that, because of very high sensitivity, do not require routine culture confirmation of negative test results. Some studies suggest that in addition to providing more timely results, these tests may be even more sensitive than standard cultures of throat swab specimens on sheep blood agar. Additional studies are ongoing to establish the benefits and limitations of these tests."
Streptococcus, group B	"Gram-positive cocci in pairs or short chains from a normally sterile body fluid provide presumptive evidence of infection with growth in culture, establishing the diagnosis." "PCR assays are available for direct testing of CSF for GBS and may expedite diagnosis."
Trichomonas vaginalis	Microscopy NAATs are the most sensitive mean of diagnosing *T vaginalis* infection and is encouraged for detection in females and males.
Vancomycin-resistant *Enterococcus*	"Selective agars are available for screening of vancomycin-resistant enterococcus from stool specimens. Molecular assays are available for direct detection of *vanA* and *vanB* genes from rectal and blood specimens to identify vancomycin-resistant enterococci."
Zika virus	NAATs - preferred method of diagnosis Trioplex real-time PCR assay Serologic testing

BCYE: buffered charcoal yeast extract; CNS: central nervous system; CSF: cerebrospinal fluid; DNA: deoxyribonucleic acid; EIA: enzyme immunoassay; FDA: Food and Drug Administration; GDH: glutamate dehydrogenase; HIV: human immunodeficiency virus; HPV: human papillomavirus; HSE: herpes simplex encephalitis; IFA: indirect fluorescent antibody; MERS-CoV: Middle East respiratory syndrome coronavirus; MSRA: methicillin-resistant *Staphylococcus aureus*; NAAT: nucleic acid amplification test; NTM: nontuberculous mycobacteria; PCR: polymerase chain reaction; PNA FISH: peptide nucleic acid fluorescent in situ hybridization; RNA: ribonucleic acid; RT: reverse transcriptase; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

5.2 In 2019, the AAP published guidelines on managing infants at risk for group B streptococcus (GBS).[58] It recommends antenatal vaginal-rectal culture performed by using a broth enrichment "followed by GBS identification by using traditional microbiologic methods or by NAAT-based methods." However, point-of-care NAAT-based screening should not be the primary method of determining maternal colonization status due to reported variable sensitivity as compared with traditional culture, as well as "because most NAAT-based testing cannot be used to determine the antibiotic susceptibility of colonizing GBS isolates among women with a penicillin allergy."

American College of Gastroenterology

6.1 In 2016, the American College of Gastroenterology published clinical guidelines on the diagnosis, treatment, and prevention of acute diarrheal infections in adults.[59] It recommended that, given that "traditional methods of diagnosis (bacterial culture, microscopy with and without special stains and immunofluorescence, and antigen testing) fail to reveal the etiology of the majority of cases of acute diarrheal infection,... the use of FDA-approved culture-independent methods of diagnosis can be recommended at least as an adjunct to traditional methods. (Strong recommendation, low level of evidence)." These are described in the rationale as multiplex molecular testing.

American Society for Microbiology

7.1 In 2020, the American Society for Microbiology updated the 2010 guidelines on detecting and identifying GBS that were originally published by the CDC, with plans to continue updating regularly.[60] The most recent update took place July 2021. The guidelines state that "intrapartum NAAT without enrichment has an unacceptably high false negative rate...As such we do not recommend the use of intrapartum NAAT without enrichment to rule out the need for prophylaxis." All GBS screening specimens should be incubated in selective enrichment broth prior to agar media plating or NAAT. "Nucleic acid amplification-based identification of GBS from enrichment broth is acceptable" for GBS screening, "but not sufficient for all patients" due to high false-negative rates.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 17.

Table 17. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT04781530[a]	ADEQUATE Advanced Diagnostics for Enhanced QUality of Antibiotic Prescription in Respiratory Tract Infections in Emergency Rooms - Paediatric	900	Sep 2024 (completed, unpublished)
NCT05759494	The Clinical and Pharmacoeconomic Impact of Rapid Diagnostic Test (Multiplex PCR FilmArray) on Antimicrobial Decision Making Compared to Conventional Decision Making Among Critically Ill Patients	100	Feb 2024 (unknown)
NCT04835818	Clinical Impact on Point-of-Care Multiplex Polymerase Chain Reaction (PCR) Testing for Critically Ill Adult Patients With Community-acquired Pneumonia	60	May 2022
NCT03840603[a]	PROARRAY: Impact on PCT+ FilmArray RP2 Plus Use in LRTI Suspicion in Emergency Department	444	Dec 2021 (unknown)
NCT04547556[a]	ADEQUATE Advanced Diagnostics for Enhanced QUality of Antibiotic Prescription in Respiratory Tract Infections in Emergency Rooms	185	May 2022 (terminated)
NCT04651712	The Effect of a Point-of-care Sputum Specimen Assay on Antibiotic Treatment of Patients Admitted Acutely With Suspected Pneumonia: A Multicenter Randomized Controlled Trial	290	Jun 2022
NCT03362970[a]	Improvements Through the Use of a Rapid Multiplex PCR Enteric Pathogen Detection Kit in Children With Hematochezia	60	Dec 2022 (completed)
NCT03895281[a]	Clinical Evaluation of the FilmArray® Meningitis/Encephalitis (ME) Panel	150	Apr 2020 (Unknown)

ISRCTN: International Standard Randomised Controlled Trial Number; NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical condition/diagnosis
  - Microorganism in question
  - Past and present testing
  - Specific test being requested
- Pertinent laboratory and imaging results

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0068U	Candida species panel (C. albicans, C. glabrata, C. parapsilosis, C. kruseii, C tropicalis, and C. auris), amplified probe technique with qualitative report of the presence or absence of each species ***(Includes MYCODART-PCR™ Dual Amplification Real Time PCR Panel for 6 Candida species, RealTime Laboratories, Inc/MycoDART, Inc)***
	0086U	Infectious disease (bacterial and fungal), organism identification, blood culture, using rRNA FISH, 6 or more organism targets, reported as positive or negative with phenotypic minimum inhibitory concentration (MIC) -based antimicrobial susceptibility ***(Includes Accelerate PhenoTest™ BC kit, Accelerate Diagnostics, Inc)***
	0096U	Human Papillomavirus (HPV), high-risk types (i.e., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68), male urine ***(Includes HPV, High-Risk, Male Urine, Molecular Testing Labs)***
	0109U	Infectious disease (Aspergillus species), real-time PCR for detection of DNA from 4 species (A. fumigatus, A. terreus, A. niger, and A. flavus), blood, lavage fluid, or tissue, qualitative reporting of presence or absence of each species ***(Includes MYCODART-PCR™ Dual Amplification Real Time PCR Panel for 4 Aspergillus species, RealTime Laboratories, Inc/MycoDART, Inc)***
	0112U	Infectious agent detection and identification, targeted sequence analysis (16S and 18S rRNA genes) with drug-resistance gene ***(Includes MicroGenDX qPCR & NGS For Infection, MicroGenDX)***
	0115U	Respiratory infectious agent detection by nucleic acid (DNA and RNA), 18 viral types and subtypes and 2 bacterial targets, amplified probe technique, including multiplex reverse transcription for RNA targets, each analyte reported as detected or not detected ***(Includes ePlex Respiratory Pathogen (RP) Panel, GenMark Diagnostics, Inc)***
	0140U	Infectious disease (fungi), fungal pathogen identification, DNA (15 fungal targets), blood culture, amplified probe technique, each target reported as detected or not detected

Type	Code	Description
		(Includes ePlex® BCID Fungal Pathogens Panel, GenMark Diagnostics, Inc)
	0141U	Infectious disease (bacteria and fungi), gram-positive organism identification and drug resistance element detection, DNA (20 gram-positive bacterial targets, 4 resistance genes, 1 pan gram-negative bacterial target, 1 pan Candida target), blood culture, amplified probe technique, each target reported as detected or not detected ***Includes ePlex® BCID Gram-Positive Panel, GenMark Diagnostics, Inc)***
	0142U	Infectious disease (bacteria and fungi), gram-negative bacterial identification and drug resistance element detection, DNA (21 gram-negative bacterial targets, 6 resistance genes, 1 pan gram-positive bacterial target, 1 pan Candida target), amplified probe technique, each target reported as detected or not detected ***(Includes ePlex® BCID Gram-Negative Panel, GenMark Diagnostics, Inc)***
	0151U	Infectious disease (bacterial or viral respiratory tract infection), pathogen specific nucleic acid (DNA or RNA), 33 targets, real-time semi-quantitative PCR, bronchoalveolar lavage, sputum, or endotracheal aspirate, detection of 33 organismal and antibiotic resistance genes with limited semi-quantitative results ***(Includes ePlex® BCID Gram-Negative Panel, GenMark Diagnostics, Inc)***
	0202U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab, each pathogen reported as detected or not detected ***(Includes BioFire® Respiratory Panel 2.1 (RP2.1), BioFire® Diagnostics, BioFire® Diagnostics, LLC)***
	0219U	Infectious agent (human immunodeficiency virus), targeted viral next-generation sequence analysis (i.e., protease [PR], reverse transcriptase [RT], integrase [INT]), algorithm reported as prediction of antiviral drug susceptibility ***(Includes Sentosa® SQ HIV-1 Genotyping Assay, Vela Diagnostics USA, Inc, Vela Operations Singapore Pte Ltd)***
	0223U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab, each pathogen reported as detected or not detected ***(Includes QIAstat-Dx Respiratory SARS CoV-2 Panel, QIAGEN Sciences, QIAGEN GmbH)***
	0225U	Infectious disease (bacterial or viral respiratory tract infection) pathogen-specific DNA and RNA, 21 targets, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), amplified probe technique, including multiplex reverse transcription for RNA targets, each analyte reported as detected or not detected ***(Includes ePlex® Respiratory Pathogen Panel 2, GenMark Dx, GenMark Diagnostics, Inc)***
	0240U	Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 3 targets (severe acute respiratory syndrome coronavirus 2 [SARS-

Type	Code	Description
		CoV-2], influenza A, influenza B), upper respiratory specimen, each pathogen reported as detected or not detected ***(Deleted code effective 7/1/2025)***
	0241U	Infectious disease (viral respiratory tract infection), pathogen-specific RNA, 4 targets (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], influenza A, influenza B, respiratory syncytial virus [RSV]), upper respiratory specimen, each pathogen reported as detected or not detected ***(Deleted code effective 7/1/2025)***
	0301U	Infectious agent detection by nucleic acid (DNA or RNA), Bartonella henselae and Bartonella quintana, droplet digital PCR (ddPCR); Includes Bartonella ddPCR, Galaxy Diagnostics, Inc
	0302U	Infectious agent detection by nucleic acid (DNA or RNA), Bartonella henselae and Bartonella quintana, droplet digital PCR (ddPCR); following liquid enhancement ***(Includes Bartonella Digital ePCR™, Galaxy Diagnostics, Inc)***
	0323U	Infectious agent detection by nucleic acid (DNA and RNA), central nervous system pathogen, metagenomic next-generation sequencing, cerebrospinal fluid (CSF), identification of pathogenic bacteria, viruses, parasites, or fungi ***(Includes Johns Hopkins Metagenomic Next-Generation Sequencing Assay for Infectious Disease Diagnostics, Johns Hopkins Medical Microbiology Laboratory)***
	0351U	Infectious disease (bacterial or viral), biochemical assays, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), interferon gamma-induced protein-10 (IP-10), and C-reactive protein, serum, algorithm reported as likelihood of bacterial infection ***(Includes MeMed BV®, MeMed Diagnostics, Ltd)***
	0369U	Infectious agent detection by nucleic acid (DNA and RNA), gastrointestinal pathogens, 31 bacterial, viral, and parasitic organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique ***(Deleted code effective 7/1/2025)***
	0370U	Infectious agent detection by nucleic acid (DNA and RNA), surgical wound pathogens, 34 microorganisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, wound swab ***(Deleted code effective 7/1/2025)***
	0371U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogen, semiquantitative identification, DNA from 16 bacterial organisms and 1 fungal organism, multiplex amplified probe technique via quantitative polymerase chain reaction (qPCR), urine ***(Includes Qlear UTI, Lifescan Labs of Illinois, Thermo Fisher Scientific)***
	0372U	Infectious disease (genitourinary pathogens), antibiotic-resistance gene detection, multiplex amplified probe technique, urine, reported as an antimicrobial stewardship risk score ***(Includes Qlear UTI - Reflex ABR, Lifescan Labs of Illinois, Thermo Fisher Scientific)***
	0373U	Infectious agent detection by nucleic acid (DNA and RNA), respiratory tract infection, 17 bacteria, 8 fungus, 13 virus, and 16 antibiotic-resistance genes, multiplex amplified probe technique, upper or lower respiratory specimen ***(Deleted code effective 7/1/2025)***
	0374U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 21 bacterial and fungal organisms and

Type	Code	Description
		identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, urine ***(Deleted code effective 7/1/2025)***
	0402U	Infectious agent (sexually transmitted infection), Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, Mycoplasma genitalium, multiplex amplified probe technique, vaginal, endocervical, or male urine, each pathogen reported as detected or not detected ***(Includes Abbott Alinity™ m STI Assay, Abbott Molecular, Inc)***
	0455U	Infectious agents (sexually transmitted infection), Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis, multiplex amplified probe technique, vaginal, endocervical, gynecological specimens, oropharyngeal swabs, rectal swabs, female or male urine, each pathogen reported as detected or not detected ***(Includes Abbott Alinity™ m STI Assay, Abbott Molecular, Inc)***
	0480U	Infectious disease (bacteria, viruses, fungi, and parasites), cerebrospinal fluid (CSF), metagenomic next-generation sequencing (DNA and RNA), bioinformatic analysis, with positive pathogen identification ***(Includes Bacteria, Viruses, Fungus, and Parasite Metagenomic Sequencing, Spinal Fluid (MSCSF), Mayo Clinic, Laboratory Developed Test)***
	0483U	Infectious disease (Neisseria gonorrhoeae), sensitivity, ciprofloxacin resistance (gyrA S91F point mutation), oral, rectal, or vaginal swab, algorithm reported as probability of fluoroquinolone resistance ***(Includes Ciprofloxacin Susceptibility of Neisseria gonorrhoeae, MedArbor Diagnostics, SpeeDx, Inc)***
	0484U	Infectious disease (Mycoplasma genitalium), macrolide sensitivity (23S rRNA point mutation), oral, rectal, or vaginal swab, algorithm reported as probability of macrolide resistance ***(Includes Macrolide Resistance of Mycoplasma genitalium, MedArbor Diagnostics, SpeeDx, Inc)***
	0500T	Infectious agent detection by nucleic acid (DNA or RNA), human papillomavirus (HPV) for five or more separately reported high-risk HPV types (e.g., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) (i.e., genotyping) ***(Deleted code effective 1/1/2025)***
	0502U	Human papillomavirus (HPV), E6/E7 markers for high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), cervical cells, branched-chain capture hybridization, reported as negative or positive for high risk for HPV ***(Includes QuantiVirus™ HPV E6/E7 mRNA Test for Cervical Cancer, DiaCarta, Inc)***
	0504U	Infectious disease (urinary tract infection), identification of 17 pathologic organisms, urine, realtime PCR, reported as positive or negative for each organism ***(Includes Urinary Tract Infection Testing, NxGen MDx LLC)***
	0527U	Herpes simplex virus (HSV) types 1 and 2 and Varicella zoster virus (VZV), amplified probe technique, each pathogen reported as detected or not detected ***(Includes Abbott Alinity™ m HSV 1 & 2 / VZV Assay, Abbott Molecular, Inc) (Code effective 1/1/2025)***
	0528U	Lower respiratory tract infectious agent detection, 18 bacteria, 8 viruses, and 7 antimicrobial-resistance genes, amplified probe technique,

Type	Code	Description
		including reverse transcription for RNA targets, each analyte reported as detected or not detected with semiquantitative results for 15 bacteria ***(Includes BIOFIRE® FILMARRAY® Pneumonia (PN) Panel, bioMérieux) (Code effective 1/1/2025)***
	0556U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific DNA and RNA by real-time PCR, 12 targets, nasopharyngeal or oropharyngeal swab, including multiplex reverse transcription for RNA targets, each analyte reported as detected or not detected ***(Includes HealthTrackRx Bronchitis, HealthTrackRx, Thermo Fisher Scientific) (Code effective 7/1/2025)***
	0563U	Infectious disease (bacterial and/or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 11 viral targets and 4 bacterial targets, qualitative RT-PCR, upper respiratory specimen, each pathogen reported as positive or negative ***(Includes BIOFIRE® SPOTFIRE® Respiratory/Sore Throat (R/ST) Panel – Respiratory Menu, bioMérieux) (Code effective 7/1/2025)***
	0564U	Infectious disease (bacterial and/or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 10 viral targets and 4 bacterial targets, qualitative RT-PCR, upper respiratory specimen, each pathogen reported as positive or negative ***(Includes BIOFIRE® SPOTFIRE® Respiratory/Sore Throat (R/ST) Panel – Sore Throat Menu, bioMérieux) (Code effective 7/1/2025)***
	0588U	Infectious disease (bacterial or viral), 32 genes (29 informative and 3 housekeeping), immune response mRNA, gene expression profiling by split-well multiplex reverse transcription loop-mediated isothermal amplification (RT-LAMP), whole blood, reported as continuous risk scores for likelihood of bacterial and viral infection and likelihood of severe illness within the next 7 days ***(Includes TriVerity™, Inflammatix™, Inc) (Code effective 10/1/2025)***
	0590U	Infectious disease (bacterial and fungal), DNA of 44 organisms (34 bacteria, 10 fungi), urine, next-generation sequencing, reported as positive or negative for each organism ***(Includes BIOTIA-ID™ Urine NGS Assay, Biotia Inc) (Code effective 10/1/2025)***
	0593U	Infectious disease (genitourinary pathogens), DNA, 46 targets (28 pathogens, 18 resistance genes), RT-PCR amplified probe technique, urine, each analyte reported as detected or not detected ***(Includes Taq Array Card Urinary Tract Infection PCR Panel, SoftCell Laboratories LLC, Doc Lab Inc) (Code effective 10/1/2025)***
	0595U	Infectious disease (tropical fever pathogens), vector-borne and zoonotic pathogens, including 2 viruses (Chikungunya virus and Dengue virus serotypes 1, 2, 3, and 4), 1 bacterium (Leptospira species), and 1 parasite with species differentiation (Plasmodium species, Plasmodium falciparum, and Plasmodium vivax/ovale), real-time RT-PCR, whole blood, each pathogen reported as detected or not detected ***(Includes BIOFIRE® FILMARRAY® Tropical Fever (TF) Panel, bioMérieux) (Code effective 10/1/2025)***
	81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (e.g., positive or negative for high probability of usual interstitial pneumonia [UIP])

Type	Code	Description
	87154	Culture, typing; identification of blood pathogen and resistance typing, when performed, by nucleic acid (DNA or RNA) probe, multiplexed amplified probe technique including multiplex reverse transcription, when performed, per culture or isolate, 6 or more targets
	87426	Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], fluorescence immunoassay [FIA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative; severe acute respiratory syndrome coronavirus (e.g., SARS-CoV, SARS-CoV-2 [COVID-19])
	87468	Infectious agent detection by nucleic acid (DNA or RNA); Anaplasma phagocytophilum, amplified probe technique
	87469	Infectious agent detection by nucleic acid (DNA or RNA); Babesia microti, amplified probe technique
	87471	Infectious agent detection by nucleic acid (DNA or RNA); Bartonella henselae and Bartonella quintana, amplified probe technique
	87472	Infectious agent detection by nucleic acid (DNA or RNA); Bartonella henselae and Bartonella quintana, quantification
	87478	Infectious agent detection by nucleic acid (DNA or RNA); Borrelia miyamotoi, amplified probe technique
	87480	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, direct probe technique
	87481	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, amplified probe technique
	87482	Infectious agent detection by nucleic acid (DNA or RNA); Candida species, quantification
	87483	Infectious agent detection by nucleic acid (DNA or RNA); central nervous system pathogen (e.g., Neisseria meningitidis, Streptococcus pneumoniae, Listeria, Haemophilus influenzae, E. coli, Streptococcus agalactiae, enterovirus, human parechovirus, herpes simplex virus type 1 and 2, human herpesvirus 6, cytomegalovirus, varicella zoster virus, Cryptococcus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets
	87484	Infectious agent detection by nucleic acid (DNA or RNA); Ehrlichia chaffeensis, amplified probe technique
	87485	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, direct probe technique
	87486	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, amplified probe technique
	87487	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia pneumoniae, quantification
	87490	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, direct probe technique
	87491	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, amplified probe technique
	87492	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, quantification
	87493	Infectious agent detection by nucleic acid (DNA or RNA); Clostridium difficile, toxin gene(s), amplified probe technique
	87495	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, direct probe technique

Type	Code	Description
	87496	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, amplified probe technique
	87497	Infectious agent detection by nucleic acid (DNA or RNA); cytomegalovirus, quantification
	87498	Infectious agent detection by nucleic acid (DNA or RNA); enterovirus, amplified probe technique, includes reverse transcription when performed
	87500	Infectious agent detection by nucleic acid (DNA or RNA); vancomycin resistance (e.g., enterococcus species van A, van B), amplified probe technique
	87501	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, includes reverse transcription, when performed, and amplified probe technique, each type or subtype
	87502	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, for multiple types or sub-types, includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, first 2 types or sub-types
	87503	Infectious agent detection by nucleic acid (DNA or RNA); influenza virus, for multiple types or sub-types, includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, each additional influenza virus type or sub-type beyond 2 (List separately in addition to code for primary procedure)
	87505	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (e.g., Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets
	87506	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (e.g., Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets
	87507	Infectious agent detection by nucleic acid (DNA or RNA); gastrointestinal pathogen (e.g., Clostridium difficile, E. coli, Salmonella, Shigella, norovirus, Giardia), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets
	87510	Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, direct probe technique
	87511	Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, amplified probe technique
	87512	Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, quantification
	87513	Infectious agent detection by nucleic acid (DNA or RNA); Helicobacter pylori (H. pylori), clarithromycin resistance, amplified probe technique ***(Code effective 1/1/2025)***
	87516	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis B virus, amplified probe technique
	87517	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis B virus, quantification
	87520	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, direct probe technique

Type	Code	Description
	87521	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, amplified probe technique, includes reverse transcription when performed
	87522	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, quantification, includes reverse transcription when performed
	87525	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, direct probe technique
	87526	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, amplified probe technique
	87527	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis G, quantification
	87528	Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, direct probe technique
	87529	Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, amplified probe technique
	87530	Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, quantification
	87531	Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, direct probe technique
	87532	Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, amplified probe technique
	87533	Infectious agent detection by nucleic acid (DNA or RNA); Herpes virus-6, quantification
	87534	Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, direct probe technique
	87535	Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, amplified probe technique, includes reverse transcription when performed
	87536	Infectious agent detection by nucleic acid (DNA or RNA); HIV-1, quantification, includes reverse transcription when performed
	87537	Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, direct probe technique
	87538	Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, amplified probe technique, includes reverse transcription when performed
	87539	Infectious agent detection by nucleic acid (DNA or RNA); HIV-2, quantification, includes reverse transcription when performed
	87540	Infectious agent detection by nucleic acid (DNA or RNA); Legionella pneumophila, direct probe technique
	87541	Infectious agent detection by nucleic acid (DNA or RNA); Legionella pneumophila, amplified probe technique
	87542	Infectious agent detection by nucleic acid (DNA or RNA); Legionella pneumophila, quantification
	87550	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, direct probe technique
	87551	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, amplified probe technique
	87552	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria species, quantification
	87555	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, direct probe technique

Type	Code	Description
	87556	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, amplified probe technique
	87557	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria tuberculosis, quantification
	87560	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria avium-intracellulare, direct probe technique
	87561	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria avium-intracellulare, amplified probe technique
	87562	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacteria avium-intracellulare, quantification
	87563	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma genitalium, amplified probe technique
	87564	Infectious agent detection by nucleic acid (DNA or RNA); Mycobacterium tuberculosis, rifampin resistance, amplified probe technique ***(Code effective 1/1/2025)***
	87580	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma pneumoniae, direct probe technique
	87581	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma pneumoniae, amplified probe technique
	87582	Infectious agent detection by nucleic acid (DNA or RNA); Mycoplasma pneumoniae, quantification
	87590	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, direct probe technique
	87591	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, amplified probe technique
	87592	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, quantification
	87594	Infectious agent detection by nucleic acid (DNA or RNA); Pneumocystis jirovecii, amplified probe technique ***(Code effective 1/1/2025)***
	87623	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), low-risk types (e.g., 6, 11, 42, 43, 44)
	87624	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), high-risk types (e.g., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68), pooled result ***(Code revision effective 1/1/2025)***
	87625	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), types 16 and 18 only, includes type 45, if performed
	87626	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), separately reported high-risk types (e.g., 16, 18, 31, 45, 51, 52) and high-risk pooled result(s) ***(Code effective 1/1/2025)***
	87631	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (e.g., adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets
	87632	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (e.g., adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets
	87633	Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (e.g., adenovirus, influenza virus, coronavirus, metapneumovirus,

Type	Code	Description
		parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets
	87634	Infectious agent detection by nucleic acid (DNA or RNA); respiratory syncytial virus, amplified probe technique
	87635	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), amplified probe technique
	87636	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]) and influenza virus types A and B, multiplex amplified probe technique
	87637	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), influenza virus types A and B, and respiratory syncytial virus, multiplex amplified probe technique
	87640	Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus, amplified probe technique
	87641	Infectious agent detection by nucleic acid (DNA or RNA); Staphylococcus aureus, methicillin resistant, amplified probe technique
	87650	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, direct probe technique
	87651	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, amplified probe technique
	87652	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group A, quantification
	87653	Infectious agent detection by nucleic acid (DNA or RNA); Streptococcus, group B, amplified probe technique
	87660	Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, direct probe technique
	87661	Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, amplified probe technique
	87662	Infectious agent detection by nucleic acid (DNA or RNA); Zika virus, amplified probe technique
	87797	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; direct probe technique, each organism
	87798	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism
	87799	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; quantification, each organism
HCPCS	G0567	Infectious agent detection by nucleic acid (DNA or RNA); hepatitis C, screening, amplified probe technique ***(Code effective 4/1/2025)***

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/01/2026	New policy.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status
In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is “experimental or investigational” by the Plan, the Plan shall refer to evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).
4. Professionals, specialists, and experts.
5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

Feedback

Blue Shield of California Promise Health Plan is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.