UnitedHealthcare | UMR

Genitourinary Pathogen Nucleic Acid Detection Testing

Policy Number: UMR2025T0608L
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➲ Instructions for Use

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Related Policies
None

Coverage Rationale

The following are proven and medically necessary to evaluate symptomatic individuals for Vaginitis:

- Direct and amplified DNA probe testing for *Trichomonas vaginalis*
- Direct probe testing for *Candida* spp.

Due to insufficient evidence of efficacy, the following are unproven and not medically necessary:

- Amplified DNA probe testing for vulvovaginitis due to *Candida* spp.
- Direct and amplified DNA probe testing for bacterial Vaginosis (i.e., *Gardnerella vaginalis*)
- Multiplex polymerase chain reaction (PCR) panel testing of genitourinary pathogens, including but not limited to pathogens commonly associated with Vaginitis
- Screening of asymptomatic individuals for Vaginitis

Note: This policy does **not** apply to tests for gonorrhea and chlamydia.

Definitions

Sexually Transmitted Infection (STI): An STI is an infection that is spread by sexual contact. Examples of STIs include chlamydia, gonorrhea, human papillomavirus (HPV), herpes, syphilis, and human immunodeficiency virus (HIV). [American College of Obstetricians and Gynecologists (ACOG), 2021]

Vaginitis: Vaginitis is defined as inflammation or infection of the vagina. The most common causes of Vaginitis include vulvovaginal candidiasis, trichomoniasis, and bacterial Vaginosis. (ACOG, 2020)

Vaginosis: Vaginosis is caused by the overgrowth of a number of organisms that are normally found in the vagina. It is a common cause of Vaginitis. (ACOG, 2020)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and

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applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
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
0330U	Infectious agent detection by nucleic acid (DNA or RNA), vaginal pathogen panel, identification of 27 organisms, amplified probe technique, vaginal swab
0557U	Infectious disease (bacterial vaginosis and vaginitis), real-time amplification of DNA markers for Atopobium vaginae, Gardnerella vaginalis, Megasphaera types 1 and 2, bacterial vaginosis associated bacteria-2 and -3 (BVAB-2, BVAB-3), Mobiluncus species, Trichomonas vaginalis, Neisseria gonorrhoeae, Candida species (C. albicans, C. tropicalis, C. parapsilosis, C. glabrata, C. krusei), Herpes simplex viruses 1 and 2, vaginal fluid, reported as detected or not detected for each organism
81513	Infectious disease, bacterial vaginosis, quantitative real-time amplification of RNA markers for Atopobium vaginae, Gardnerella vaginalis, and Lactobacillus species, utilizing vaginal-fluid specimens, algorithm reported as a positive or negative result for bacterial vaginosis
81514	Infectious disease, bacterial vaginosis and vaginitis, quantitative real-time amplification of DNA markers for Gardnerella vaginalis, Atopobium vaginae, Megasphaera type 1, Bacterial Vaginosis Associated Bacteria-2 (BVAB-2), and Lactobacillus species (L. crispatus and L. jensenii), utilizing vaginal-fluid specimens, algorithm reported as a positive or negative for high likelihood of bacterial vaginosis, includes separate detection of Trichomonas vaginalis and/or Candida species (C. albicans, C. tropicalis, C. parapsilosis, C. dubliniensis), Candida glabrata, Candida krusei, when reported
81515	Infectious disease, bacterial vaginosis and vaginitis, real-time PCR amplification of DNA markers for Atopobium vaginae, Atopobium species, Megasphaera type 1, and Bacterial Vaginosis Associated Bacteria-2 (BVAB-2), utilizing vaginal-fluid specimens, algorithm reported as positive or negative for high likelihood of bacterial vaginosis, includes separate detection of Trichomonas vaginalis and Candida species (C. albicans, C. tropicalis, C. parapsilosis, C. dubliniensis), Candida glabrata/Candida krusei, when reported
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
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
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
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
87800	Infectious agent detection by nucleic acid (DNA or RNA), multiple organisms; direct probe(s) technique
87801	Infectious agent detection by nucleic acid (DNA or RNA), multiple organisms; amplified probe(s) technique

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Description of Services

Bacterial vaginosis (BV), *Trichomonas vaginalis* (*T. vaginalis* or TV), and *Candida* species cause the highest number of cases of acute vulvovaginal symptoms that lead a woman to seek medical care [Centers for Disease Control (CDC), 2021]. The physician must assimilate information from the history and physical examination with information obtained from a vaginal swab to make a diagnosis for the appropriate treatment. Material from the swab can be used to make a determination of vaginal pH, to prepare slides for microscopy, to perform molecular tests and other rapid tests, and to culture organisms.

Molecular testing for diagnosis of vaginal infection is based on the detection of one or more specific nucleic acid sequences. In the United States, most molecular assays currently available for Vaginitis/Vaginosis are direct DNA probe tests and nucleic acid amplification tests (NAATs). (Coleman and Gaydos, 2018)

The potential use of nucleic acid probe technology for the diagnosis of Vaginitis/Vaginosis was explored in the mid-1990s with the development of a DNA probe assay. Several manufacturers have now developed NAATs and panel assays using Polymerase Chain Reaction (PCR) which can detect multiple pathogens. For example, Affirm™ VPIII, a commercially available DNA probe test, utilizes hybridization of specific organismal sequences to specific labeled DNA probes to detect *Candida* species, *Gardnerella vaginalis* (as a marker for BV), and *Trichomonas vaginalis*.

Clinical Evidence

Common Causes of Vaginitis

The most common causes of vaginitis include trichomoniasis, bacterial vaginosis (BV), and vulvovaginal candidiasis (VVC). Table 1 describes the main features of these three causes.

Table 1. Features of Vaginitis/Vaginosis

Infection	Discharge	Whiff test	pH	Microscopy
Candida species	Thick	Negative	Normal (< 4.5)	Yeasts, hyphae
Bacterial vaginosis	Thin, homogeneous	Positive	Increased (> 4.5)	Clue cells, decreased Lactobacilli
Trichomonas vaginalis	Frothy, yellow-green	Positive	Increased (> 4.5)	Protozoa

Diagnosis of vaginitis/vaginosis typically hinges on the proper evaluation of a significant amount of data, including the information presented in the table above, and can be quite time-consuming. Despite the frequency with which women present to their doctors with complaints of vaginal symptoms, physicians do not always reliably carry out the diagnostic protocol (Schwiertz et al., 2006). Correct, timely identification of pathogens is critical for treatment, prevention of the spread of contagious disease, and reduction in the risks associated with vaginal infection.

Bacterial Vaginosis (BV)

BV is the most common documented cause of vulvovaginitis among women of reproductive age. In the United States, the prevalence of BV in the general population is estimated to be almost one in three women (Allsworth and Peipert, 2007). BV can produce vaginal discharge and a “fishy” odor, but the majority of women are asymptomatic (Koumans et al., 2007). BV is a polymicrobial infection that is characterized by a shift in vaginal microbiota from an acidic pH (< 4.5) with *Lactobacillus* species to a more alkaline pH heralded by the presence of *Gardnerella vaginalis*, a gram-variable coccobacillus, and marked by the presence of other species including *Prevotella, Mobiluncus, Ureaplasma*, and *Mycoplasma*.(Jones, 2019)

BV is of significant public health interest, not just because of its high prevalence, but because it is associated with an increased risk of other medical complications including preterm labor and pelvic inflammatory disease along with increased risk to acquire sexually transmitted infections (Paavonen and Brunham, 2018). Despite its association with adverse pregnancy outcomes, the United States Preventive Services Task Force (USPSTF, 2020) does not currently recommend screening of asymptomatic pregnant women for BV although workup of symptomatic women is recommended. BV can be successfully treated with antibiotics, though the recurrence rate is high. BV can be sexually transmitted and is one of the most commonly diagnosed infections in women following sexual assault. Treatment of sexual partners does not decrease the recurrence rate. (CDC, 2021)

Diagnosis of BV using clinical criteria may be performed by assessing a patient sample via wet prep microscopy for at least three of the four Amsel’s criteria: thin and homogeneous vaginal discharge, pH > 4.5, positive whiff test, and

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presence of clue cells on microscopy. These criteria are indicative of the microbiota changes associated with BV which allow overgrowth of species such as *Gardnerella vaginalis* (*G. vaginalis*). The vaginal Gram stain is considered the reference standard for BV diagnosis and evaluates the quantity of normal flora versus BV flora. Gram stains may be used in conjunction with Nugent scoring to categorize them as being normal flora (0-3), intermediate/mixed flora (4-6), or indicative of BV (7-10). Due to low sensitivity and specificity, the CDC does not recommend the use of Pap smear for the diagnosis of BV. Bacterial culture of *G. vaginalis* is also not recommended as it is nonspecific. (CDC, 2021)

Muzny et al. (2022) summarized literature pertaining to BV that was used for the CDC advisory group's development of the 2021 CDC sexually transmitted infections (STIs) treatment guidelines. The literature reviewed for the guideline addressed epidemiology, diagnosis, and management of STIs overall, while the Muzny et al. summary focuses on updates related to BV specifically, including focus on global epidemiology, risk factors, molecular diagnostic tests, novel treatment regimens and data supportive of sexual transmission of BV-related bacteria. The authors note that since the publication of the 2015 CDC STD treatment guidelines, no new point-of-care tests for BV diagnosis are available. Existing point-of-care tests mentioned are wet mount, Gram stain/Nugent score, OSOM® BV Blue® test, FemExam® card and Affirm™ VPIII assay. Five commercially available nucleic acid amplification tests (NAATs) including BD Max™ Vaginal Panel, Hologic Aptima® BV, LabCorp NuSwab® VG, MDL OneSwab® BV panel PCR and Quest Diagnostics SureSwab® BV are available. Of these, the BD Max Vaginal Panel and Aptima BV by Hologic are FDA-approved. The other tests are noted to have been internally validated and shown to have good sensitivity and specificity, similar to the FDA-approved assays. BD Max Vaginal Panel has demonstrated 90.5% sensitivity and 85.8% specificity for BV diagnosis when compared to Amsel criteria and Nugent score (test also provides results for *Candida* spp. and *T. vaginalis* with sensitivities of 94.1% and 93.1%, respectively and specificities of 99.7% and 99.3%, respectively). The Aptima BV test has sensitivity ranging from 95% to 97.3% and specificity ranging from 85.8% to 89.6% when compared to Nugent score (including Amsel criteria for intermediate Nugent scores). Range is dependent on the use of clinician-collected versus patient-collected vaginal swabs. Secondary analysis of the Aptima BV test reportedly revealed a higher sensitivity and specificity than in-clinic testing using Amsel criteria and clinician diagnosis. The article's authors indicate there are some advantages to using NAAT over point-of-care tests for BV, including the ability to distinguish specific bacteria, enable quantitation, maintain objectiveness, and provide the ability for individuals to self-collect. Further, NAATs do not require the use of microscopy, which requires training, expertise, and upkeep of equipment. That said, traditional means of diagnosing BV, including Amsel criteria and Nugent score, remain useful tools for diagnosis as they provide rapid results (and therefore rapid treatment) and can be done at lower cost. In conclusion, the authors note that additional research to investigate causes of BV is needed; this may improve prevention, diagnosis, and treatment of BV.

A study designed to evaluate agreement among observers reviewing Gram stains for a diagnosis of BV found complete agreement among reviewers in 76.2% of cases (Mohanty et al., 2010). Another study used κ chance-corrected agreement statistics to compare the microscopic diagnosis of *Candida* and BV on wet prep by blinded pairs of observers; the study found agreement was moderate ($\kappa = 0.45$) for BV and fair ($\kappa = 0.3$) for VVC in a ranking system with possible outcomes of almost perfect, substantial, moderate, fair, and poor agreement. (Whiteside et al., 2011)

Trichomonas Vaginalis (TV)

Trichomoniasis is caused by a microscopic organism called *Trichomonas vaginalis* (*T. vaginalis* or TV). TV is a sexually-transmitted motile protozoan that causes vaginal discharge and pruritus, although the majority of cases are believed to be asymptomatic. The characteristic appearance of the cervix associated with this infection, strawberry cervix, only occurs in a small number of cases and therefore is an inconsistent diagnostic feature. (Huppert, 2009)

TV is considered a sexually transmitted disease, and concurrent treatment is important for the index case and all sexual partners to eradicate infection. Like BV, TV is one of the most common infections following sexual assault. Due to the high rate of reinfection with TV, the CDC recommends retesting within 3 months following initial treatment for all sexually active women. (CDC, 2021)

Successful treatment of TV is important because it has been associated with infertility and adverse pregnancy outcomes. Further, because TV has been associated with increased vaginal shedding of HIV, screening of all HIV-positive women entering care is recommended by the CDC. TV can also cause cervicitis, leading to vaginal discharge, and the CDC recommends women with cervicitis who are symptomatic for infection should have additional testing if trichomonads are not identified by microscopy. (CDC, 2021)

Although the characteristic flagellated organisms can be visualized moving about on wet prep, the sensitivity and specificity for the diagnosis of TV on wet prep is low compared to culture. In a study comparing diagnostic modalities for the diagnosis of TV, wet mount detected 56% of infections and rapid test plus wet mount increased detection to 86% (Pattullo et al., 2009). While culture is a reliable diagnostic modality, it takes as many as five days for results (Huppert,

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2009) and is no longer the gold standard for TV diagnosis since the advent of valid molecular diagnostic methods. (CDC, 2021)

Vulvovaginal Candidiasis (VVC)

In the United States, *Candida albicans* (*C. albicans*) is responsible for most cases of VVC, followed by *Candida glabrata*. *C. albicans* is a fungus that is part of the normal flora of the oral cavity, gastrointestinal tract, and female genital tract. Morphologically, it grows as yeast and a hyphal form in contrast to *Candida glabrata*, which lacks hyphal elements. VVC symptoms are nonspecific and typically include vulvar pruritus, vulvovaginal irritation, and a thick curdy discharge. (Achkar and Fries, 2010)

Candida is usually not sexually transmitted, and VVC can occur spontaneously or as a result of a clinical risk factor such as antibiotic therapy. The true prevalence of VVC is somewhat obfuscated due to the availability of over-the-counter therapies (Sobel, 2007) which allow self-diagnosis and treatment but can also result in delay of correct diagnosis and treatment due to erroneous self-diagnosis (Ferris et al., 2002). It is estimated that 75% of women will have at least one instance of VVC in their lifetime. Treatment of uncomplicated cases is usually by topical azoles or oral fluconazole. Long-term fluconazole therapy is used for individuals with recurrent VVC, defined as three or more cases in less than one year. (CDC, 2021)

Diagnosis of VVC may be made when a woman presenting with symptoms of vaginitis has either 1) a Gram stain or wet prep of vaginal discharge that demonstrates budding yeasts, hyphae, or pseudohyphae or 2) culture or other test is positive for *Candida*. While KOH preps and Gram stains demonstrate budding yeasts, *Candida glabrata* does not form hyphae or pseudohyphae and thus may escape microscopic diagnosis (CDC, 2021). Pap tests are even less sensitive than wet prep for *Candida* species. Patients often treat themselves with over-the-counter antimycotics based on empiric diagnosis of *Candida*, but a study that offered clinical testing to women purchasing antimycotics found that only 33.7% of them actually had *Candida*. (Ferris et al., 2002)

DNA Probe Testing

DNA probe testing for *Trichomoniasis vaginalis* or *Candida* spp. may be beneficial for evaluating symptomatic women for vaginitis. There is limited evidence to demonstrate the clinical utility of direct and amplified DNA probe tests for BV and amplified DNA probe tests for vulvovaginitis due to *Candida* spp.

In a 2023 (updated 2024) Hayes molecular test assessment addressing multitarget panels for the identification of vaginal pathogens, testing via use of an enzyme-linked probe to generate visible color bound to nonamplified nucleic acids (e.g., BD Affirm VPIII panel), no peer-reviewed studies evaluating clinical benefit of multitarget panels for the detection of vaginal pathogens were identified. Per Hayes, the overall quality of evidence for these tests is low and does not address whether multitarget testing affects treatment decisions, decreases inappropriate therapy, or improves clinical outcomes.

In a 2022 Clinical Evidence Assessment, ECRI found inconclusive evidence supporting the use of the Affirm VPIII test for diagnosis of vaginitis. Available evidence indicated moderate sensitivity and specificity of Affirm VPIII for BV, but poor sensitivity for VVC and TV, although specificity was high. Additional evidence is required to evaluate the performance of Affirm VPIII compared to other diagnostic tests for vaginitis.

In a comparison of Affirm VPIII to liquid-based Pap test, Levi et al. (2011) reviewed 431 cases where material for Pap test and Affirm testing were simultaneously obtained. Affirm VPIII identified more cases of infection with all three etiologic agents than did Pap test. Using κ statistics, there was poor agreement between Pap test and Affirm VPIII for diagnosis of bacterial vaginosis and TV. Of note, Affirm VPIII identified 30 cases of coinfection by two or more organisms whereas Pap test only identified coinfection in 5 cases. This study demonstrates that Affirm VPIII may be useful for detecting mixed infection. According to the authors, this study was limited because they were not able to estimate the sensitivity and specificity of the Affirm VPIII assay and Pap tests due to not comparing their results with the gold standards such as microbial cultures or Gram stain.

In a study of 535 military women presenting with symptoms of acute vulvovaginitis (Lowe et al., 2009), vaginal specimens were collected for DNA probe analysis by Affirm VPIII. Participants were treated based on the results of wet prep microscopy, whiff test, and pH determination only and not on the basis of the molecular tests. Follow-up telephone calls were made to assess resolution of symptoms. Of 64 cases that were negative by clinical exam, DNA probe analysis detected four cases of VVC, 21 cases of BV, and three cases of mixed BV and VVC. Eight of 28 women complaining of symptoms not resolved after the clinic visit represented missed cases of BV. This study highlights that Affirm VPIII has the potential to decrease the number of repeat visits to establish a definitive diagnosis. Study limitations include its observational nature and small subgroup size for TV.

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DNA probe-based tests hybridize nucleic acid probes to unamplified pathogen DNA in vaginal samples and may be particularly useful for physicians who are less skilled in office laboratory diagnostic techniques for vaginitis. The potential value of DNA probe tests for aiding in the diagnosis of vaginosis was demonstrated by Ferris and colleagues (1995) in a study that compared the performance of routine primary care physician-performed office laboratory diagnostic techniques for women with abnormal vaginal symptoms to the results obtained by a DNA probe test for *T. vaginalis, Gardnerella vaginalis, and Candida species* (Affirm VP III). The clinical microscopic results for sensitivity and specificity were vulvovaginal candidiasis (VVC) 39.6% and 94 %, trichomoniasis 75.0 % and 96.6 %, and bacterial vaginosis (BV) 76.5 % and 70.8 %. By comparison, the sensitivity and specificity of the DNA probe test for VVC was 75.0 % and 95.7 %, trichomoniasis was 86.5 % and 98.5 %, and BV was 95.4 % and 60.7 %. The researchers concluded that primary care physicians demonstrated a high specificity but low sensitivity when identifying trichomoniasis and VVC by microscopic techniques, and that the DNA probe test was more accurate. However, each pathogen associated with common genitourinary pathogens has its own diagnostic and clinical considerations (Table 1) that in turn influences the clinical utility of the DNA probe tests.

Amplified Probe and Polymerase Chain Reaction (PCR) Panel Testing

Studies demonstrating clinical utility of panel testing for multiple genitourinary pathogens are lacking. Each of the clinical presentations of these infections is different for the various pathogens and there are unique single tests available. NAAT has limitations when applied to organisms that potentially form part of the normal human flora (Bursle and Robson, 2016) as it may lead to overdiagnosis.

While the clinical presentations and diagnostic criteria differ depending on the pathogens associated with vaginitis (Table 1), panels that screen for multiple pathogens simultaneously have been developed. Examples of commercially available multitarget PCR tests include BD MaxVaginal Panel, Hologic Aptima BV, Medical Diagnostic Laboratories (MDL) OneSwab BV panel, Quest SureSwab, LabCorp NuSwab, and Xpert® Xpress MVP. These tests are designed to detect nucleic acid sequences from microorganisms whose presence or absence is informative in the diagnosis of vaginitis/BV but differ somewhat in which indicator organisms were selected for the panel, as well as in sensitivity and specificity metrics.

A 2023 Hayes molecular test assessment focused on the evaluation of multitarget panels for the identification of vaginal pathogens. Methodologies including qualitative PCR amplification of nucleic acid targets (e.g., Xpert Xpress MVP), quantitative or semiquantitative PCR amplification of nucleic acid targets (BD Max Vaginal, Seegene Allplex™, NuSwab) and quantitative transcription-mediated amplification of nucleic acid targets (e.g., SureSwab) were addressed. Hayes found an overall low-quality body of evidence lacking studies which address clinical utility of this testing for vaginal pathogens. No evidence was identified which focused on the impact of multitarget testing on decisions regarding therapy, clinical outcomes, or the avoidance of inappropriate treatment. Furthermore, multitarget panel testing requires laboratory processing which takes longer than standard point-of-care testing and may delay definitive diagnosis.

Amor et al. (2024) conducted a comparative study to evaluate the effectiveness of the Vaginal Panel Real-Time PCR kit against traditional diagnostic methods for bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and trichomoniasis. A total of 1011 vaginal swab specimens were analyzed. The routine diagnostic method for BV was the Gram stain-based Nugent score. VVC was detected by culture, and Candida species were identified using MALDI-TOF MS. Trichomonas vaginalis was identified by culture in a selective medium. Molecular analyses were performed using the MagXtract® 3200 System and analyzed with the CFX96™ Real-Time PCR Detection System. The sensitivity, specificity, positive predictive value, and negative predictive value of the qPCR test compared to the reference method for BV diagnosis were 93.1%, 88.8%, 90.1%, and 92.2%, respectively, with a Kappa value of 0.82. For Candida species, the sensitivity, specificity, positive predictive value, and negative predictive value were 96.0%, 98.4%, 95.3%, and 98.7%, respectively. The qPCR test detected 32 additional positive samples for Candida not reported by routine diagnostics. For trichomoniasis, the qPCR test identified T. vaginalis in fifteen specimens, despite no microscopic detection in cultured specimens. While the study showed encouraging results, it has several limitations including the following: Direct comparison of BV diagnosis could not be established due to different classifications of vaginal microbiota between methods; only one vaginal swab was collected and retested after standard diagnostics, which may have affected the detection rate of the NAAT methods; for T. vaginalis, only discordant samples were analyzed using the GeneProof Trichomonas vaginalis PCR Kit; and lastly, the anonymity of the participants limited access to information about symptoms, ethnicity, contraceptive use, STI status, or menopausal state. Given these limitations, additional studies are necessary to confirm the full diagnostic accuracy of the PCR kit.

The Xpert Xpress MVP test (MVP) is a qualitative *in vitro* PCR test designed to detect DNA targets from anaerobic bacteria present in BV, TV, and *Candida* species associated with VVC through an automated system which allows an untrained operator to run a test sample with results available in less than an hour. In a prospective, observational, method comparison clinical study, Lillis et al. (2023) assessed MVP using clinician collected vaginal swabs (CVS) and self-

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collected vaginal swabs (SVS). Both sample types were collected in a clinical setting. The study took place at 12 facilities (including point-of-care settings) in geographically diverse locations in the United States and included individuals 14 years of age or older who exhibited signs/symptoms of vaginitis or vaginosis. A total of 1478 individuals were eligible to be evaluated for at least 1 of the 4 MVP reportable results. Results of testing with MVP for BV were compared to the BD Max Vaginal Panel (BDVP), while results for *Candida* group and *Candida glabrata* and *Candida krusei* targets (species not differentiated) were compared to yeast culture followed by mass spectrometry for identification of species. A composite method including results from BDVP and InPouch TV culture were the comparison method used to assess MVP TV results. These comparisons yielded high positive percent agreement which ranged from 93.6 to 99% as well as negative percent agreement ranging from 92.1% to 99.8% for both CVS and SVS samples. The authors concluded that based on this evaluation, MVP may be a helpful tool for diagnosis and subsequent treatment of vaginitis/vaginosis in laboratory and point-of-care settings. This study was sponsored by the test manufacturer; the sponsor (Cepheid) was involved in the study design and conduction as well as the collection of data and interpretation of the data, creating potential for bias. Additional large, high-quality studies demonstrating clinical utility are needed to support the use of the MVP in clinical settings.

A 2023 publication by Navarathna and colleagues described their retrospective analysis of the diagnostic performance of DNA probe-based and PCR-based molecular testing for vaginitis. The study was performed in a single Texas-based institution and took place from September 2015 to January 2023. A total of 8878 deidentified orders for DNA probe-based identification and 10,464 deidentified orders for molecular panel identification were analyzed. Testing platforms used were the BD Affirm VPIII (DNA probe test) and the BD Max MVP (qualitative *in vitro* testing using PCR). Reported results indicated no difference in the identification of TV between the two testing platforms with both populations found to have approximately 2% positivity and 61% negativity. For BV, BD Max MVP had lower positivity than BD Affirm (23% and 30%, respectively). Estimated mean proportion of positive tests for BD Affirm was 0.300 (0.290–0.309) compared to 0.234 (0.226–0.243) for BD Max MVP, with an estimated mean difference in proportion of positive tests of 0.066 (0.053–0.078). For vaginal candidiasis, however, BD Max MVP reported more diagnoses of vaginal candidiasis than BD Affirm (approximately 13.5% vs 6%, respectively). The estimated mean proportion of BD Affirm positivity was 0.063 (0.058–0.069) compared to 0.136 (0.130–0.143) for BD Max MVP, with estimated mean difference of 0.073 (0.065–0.081). Overall, the researchers concluded that data from this study indicates that BD Max MVP has lower rates of positivity for BV when compared to BD Affirm, but higher rates of positivity for vaginal candidiasis, with similar rate of detection for TV. In addition, ability to differentiate *Candida* species when using BD Max MVP allows clinicians ability to select appropriate treatment if indicated, but it could also lead to overtreatment. Ultimately, the authors endorse the use of these molecular tests for confirmation of clinical suspicion rather than screening. In addition to the retrospective design of this analysis, limitations included the lack of side-by-side comparison and the assumption that the two sample groups would have identical chances of detection with the only difference being methodology.

In a comparative study, Danby et al. (2021) sought to evaluate the performance of NAAT for use in diagnosing VVC, BV and TV. A total of 300 women, 200 of whom had vulvovaginal symptoms, were enrolled in the study and underwent vaginal swabbing. Swabs were evaluated using wet mount microscopy, culture for yeast, Gram staining, TV culture and NAAT (using NuSwab). For VVC, sensitivity was 48.5% with microscopy, 92.4% with NAAT and 83.3% with culture. For TV, sensitivity was 75% for microscopy, 100% for NAAT and 93.8% for culture. For BV, sensitivity with use of clinical criteria (Amsel criteria) was 98.7%, Gram stain was 82.7% and NAAT was 78.7%. Concordance rates between culture and NAAT were high for *Candida* at 91%; between Gram stain and NAAT for detecting BV, concordance rate was 88%. Of the women with no symptoms, 20%-21% had positive Gram stain or NAAT results and based on culture or NAAT, 8%-13% showed colonization with *Candida*. The researchers recommend consideration of the use of NAAT when evaluating individuals with vaginitis who test negative by microscopy. In this study, Amsel criteria was most accurate for diagnosis of BV, but NAAT is preferred for detecting TV and was comparable with performance of culture for individuals with VCC.

The results of a prospective, single-center, cross-sectional study aiming to validate the Seegene Allplex Vaginitis assay for use in diagnosing VVC, BV and TV were published by Vieira-Baptista et al. in 2021. The researchers recruited 758 symptomatic and asymptomatic individuals ages 18-60 years and compared the results of the Seegene assay to reference standards (Nugent score for BV, cultures for yeast and NAAT for TV). Performance of the test specific to post-menopausal and symptomatic individuals was a secondary objective of the study. Diagnosis of vaginitis was identified in 14% of participants with overall rates of BV at 22.3%, *Candida* spp. at 13.2% and TV at 2.4%. For BV, the sensitivity of the assay was found to be 91.7% and 86.6%, respectively. For any *Candida* spp., results were 91.1% and 95.6%, and for TV, the results were 94.4% and 99.9%. Test performance was precisely the same for individuals that had vulvovaginal symptoms and those who did not, and multiple infections did not appear to impact performance of the test. The authors concluded that the Seegene Allplex Vaginitis assay showed excellent performance when used for diagnosing BV and *Candida*. Although the results for TV were positive, the prevalence of TV in this study was very low and thus, the study was underpowered for this outcome.

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In an effort to compare the performance of clinical assessment with molecular detection using a vaginal panel assay, Broache et al. (2021) evaluated 489 participants in a prospective, cross-sectional, multi-center study. Clinical diagnosis occurred at the time of the visit with no knowledge of results of the vaginal panel assay and was based on signs and symptoms and wet mount microscopy. Positive percent agreement between clinical diagnosis and vaginal panel assay was 59.9% for BV, 53.5% for VVC and 28.0% for TV. Negative percent agreement was 80.2% for BV, 77.0% for VVC and 99.8% for TV. Sixty-five percent of participants with BV, 44% of participants with VVC and 56% of participants with TV by panel assay were not treated for vaginitis based on clinical assessment and diagnosis. False-positive rates of 19.8% for BV, 23.0% for VVC and 0.2% for TV were found in the comparison between clinical diagnosis and assay results, leading to potential overtreatment. The study also showed a significant difference in paired proportions between the panel test and clinical diagnosis specific to BV, suggesting that diagnosis of BV may vary depending on the type of in-clinic testing available and subjectivity when using Amsel's criteria. The researchers point out that while Gram stain with Nugent scoring is the reference standard for BV and culture is the reference standard for VVC, challenges exist with these modalities, including the lack of availability of Gram stain at some clinics and the potentially lengthy turnaround time for culture. As such, the authors concluded that use of vaginal panel assay could improve accuracy in diagnosis of vaginitis and help facilitate more timely and appropriate treatment. They recommend future studies to determine whether utilization of vaginal panel assay reduces overall rate of vaginitis return visits. Of note, the study was sponsored by Becton, Dickinson and Company, makers of the BD Max Vaginal Panel test, creating potential for bias.

Hillier et al. (2021) conducted an observational study on women seeking routine care for vaginitis. The study included 303 symptomatic women from eight clinics. Participants were assessed and treated according to the discretion of the clinician provider and the practice algorithms in their clinical setting. The researchers note that standard point-of-care tests including wet mount microscopy, vaginal pH, and potassium hydroxide/whiff were rarely performed (17%, 15%, and 21%, respectively.) As part of the study, five vaginal swabs (one of which was cryopreserved) were collected for FDA approved NAAT for vaginosis/vaginitis with the BD Max Vaginal Panel (MAX VP), Nugent scoring for BV, yeast culture for VVC and NAAT for TV. Results of this laboratory testing were not provided to either the evaluating clinician or the study enrollees. Of the 303 women, 290 had samples that could be evaluated. Results of standard laboratory-based testing were compared with MAX VP results. For BV, there was 88% concordance between the two tests (Nugent Gram stain score n = 104 and MAX VP n = 107) and 30% of all women were positive for BV by both tests. Cultures for yeast found more *Candida* than NAAT (124 vs. 99, respectively) and 32% of the women tested had one of the *Candida* species group (*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. dubliniensis*) by both culture and NAAT. Culture and NAAT testing were in agreement 90% of the time for the *Candida* species group (112 positive with culture, 92 positive with MAX VP). TV results showed 100% concordance between the two NAAT tests. Of note, laboratory-confirmed testing revealed that 10% of the women evaluated had mixed infections and 41% had no vaginal infections detected. Overall, 170 women had a laboratory-diagnosed cause for vaginitis. Of these, 47% received at least one inappropriate prescription. Antibiotics or antifungals were prescribed in 34% of women who did not have BV, TV, or VVC. Women without infectious vaginitis who were treated empirically were more likely to return for vaginitis symptoms than those who did not receive treatment (9/41 vs 5/79, $p = .02$). Ultimately, the researchers found that most assessments for vaginitis in these community practice settings did not include the use of recommended point-of-care tests and 42% of women with vaginitis symptoms received inappropriate treatment. Based on these findings, the authors concluded that different models of care may be needed for woman with symptoms of vaginitis, including sensitive and specific laboratory testing and careful patient evaluation to reach an accurate diagnosis.

Kim et al. (2020) performed a two-year, retrospective cohort study examining the utility of testing for TV by wet mount or NAAT in the routine prenatal setting. Of a total of 3,265 pregnant women, 2,489 individuals were tested for TV; 1,808 (55%), 1,661 (51%) and 980 (30%) were testing by wet mount, NAAT, or both methods, respectively. Microscopy yielded a sensitivity of 26% compared to NAAT, and a specificity of 99%. The overall prevalence of trichomoniasis was 15% by either testing method. The researchers also determined that the risk factors for trichomoniasis included younger age (aRR 0.97, $p < .01$), being of Black race (aRR 2.62, $p < .01$), abnormal vaginal discharge (aRR 1.45, $p < .01$), and chlamydia during the current pregnancy (aRR 1.70, $p < .01$).

Schwebke et al. (2020) performed a prospective, multicenter clinical study to validate the performance of an *in vitro* diagnostic transcription-mediated NAATs for the diagnosis of BV, VVC, and TV. Clinician and patient obtained swab samples were collected from symptomatic women and were tested using the Aptima BV and Aptima *Candida/Trichomonas vaginitis* (CV/TV) assays. Results were compared to Nugent (plus Amsel for intermediate Nugent) scores for BV, *Candida*, and DNA sequencing for VVC, and a composite of NAAT and culture for TV. There were 1,519 subjects enrolled. Clinician collected samples for the investigational tests revealed a 95.0% sensitivity and 89.6% specificity for BV; a 91.7% sensitivity and 94.9% specificity for *Candida*; 84.7% sensitivity and 99.1 % specificity for *C. glabrata*; and a 96.5% sensitivity and 95.1% specificity for TV. Similar results were observed from the patient collected samples. Clinician diagnosis, in-clinic assessments and investigational assay results were compared with gold standard reference methods in a secondary assessment. This secondary assessment for BV resulted in a sensitivity of ≥ 96.2%

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and specificity of ≥ 92.4% for the investigational-assay samples compared to 83.4% and 85.5% for clinicians' diagnoses, 75.9% and 94.4% for original Amsel criteria, 81.1% and 90.1% for modified Amsel criteria, and ≤ 82.8% and ≤ 91.1% for any of the individual Amsel criterion components (vaginal pH, clue cells, and whiff test). For VVC due to the *Candida* species group or *C. glabrata*, sensitivity and specificity were ≥ 91.2% and ≥ 98.9%, respectively for the investigational-assay samples compared to ≤ 27.9% and ≤ 56.4% for potassium hydroxide testing and ≤ 54.9% and ≤ 85.5% for clinicians' diagnoses. For trichomoniasis, sensitivity was ≥ 96.4% for the investigational-assay samples compared to 78.8% for culture and 38.1% for clinicians' diagnoses; specificity estimates were greater than 95% for all trichomoniasis detection methods. The authors reported that overall, the investigational tests revealed a higher sensitivity and specificity for detecting and diagnosing the causes of vaginitis compared to traditional methodologies for diagnosis. Study limitations included lack of diversity with regard to ethnic groups and high specificity of molecular testing, impacting sensitivity to disease attributable to minor species (e.g., *Prevotella*, *Candida krusei*), which were not included in assay design.

Thompson et al. (2020) conducted a study to examine the performance of the BD Max Vaginal Panel (MAX VP) compared to BD Affirm VPIII (Affirm), noting Affirm to be the "standard of care". Four vaginal swabs were collected from each of 200 symptomatic participants. *Candida* culture, Gram stain and Nugent scoring and the Hologic Aptima *Trichomonas vaginalis* assay were used as part of the analysis. When at least two tests were positive for any vaginitis target, the results were considered true positive. Sensitivity and specificity of MAX VP for BV was 96.2% and 96.1%, respectively. For Affirm, sensitivity and specificity for BV were 96.2% and 81.6%, respectively. The sensitivity of MAX VP for *Candida* spp. was 98.4% and specificity was 95.4% whereas sensitivity for Affirm was 69.4% and specificity was 100%. Lastly, MAX VP and Affirm were 100% concordant in the detection of TV. The authors concluded that MAX VP showed better accuracy when compared to Affirm for detection of *Candida* spp. and BV, and the two tests were equally accurate for detection of TV. The study was limited by its small sample size.

The clinical validity of a PCR-based assay for BV detection was conducted by Cartwright et al. (2018) during a multicenter investigational study. PCR results from 1,579 individuals were compared to Nugent Gram stain samples and a clinical evaluation following utilization of the Amsel criteria; next-generation sequencing was used to confirm conflicting results. Nugent Gram stain with Amsel criteria (used to resolve intermediate samples), yielded a prevalence of BV in the study population 34.1%. Of the 1579 samples tested, 579 (36.7%) were determined to be BV positive, 905 (57.3%) BV negative, and 95 (6.0%) BV indeterminate by PCR. Overall agreement between BV-PCR and the Nugent/ Amsel algorithm, after exclusion of BV-PCR indeterminate samples, was 92.2% (1368/1484). Using the Nugent/Amsel algorithm as the reference standard, the BV-PCR assay had a sensitivity of 96.0%, a specificity of 90.2%, a positive predictive value of 83.4%, and a negative predictive value of 97.8%. Following the resolution of conflicting results, the BV-PCR assay had a reported sensitivity of 98.7%, a specificity of 95.9%, a positive predictive value of 92.9% and a negative predictive value of 96.9%. The limitations of current methods for diagnosing BV were a confounder in this and other studies conducted on nucleic acid amplification-based assays. Researchers leading this study attempted to address this issue using an alternate molecular approach to resolve differences between the Nugent/Amsel algorithm and BV-PCR. They state that adoption of a standardized scoring system to define the microflora consistent with BV would be a logical step forward to improve accuracy of reference methods. Another limitation is that all authors of this study were employees of the study sponsor.

Schwebke and colleagues (2018) analyzed the BD MAX vaginal panel compared to reference for detection of BV, *Candida* spp., and TV. Specimens from 1,740 women were analyzed using the BD MAX panel. Clinician diagnosis (Amsel's test, KOH preparation, and wet mount) were also performed. All testing methods were compared to the respective reference methods. The BD MAX panel resulted in significantly higher sensitivity and negative predictive value than clinician diagnosis. In addition, this test showed a statistically higher overall percent agreement with each of the three reference methods than did clinician diagnosis. The authors concluded that findings from the current study supported the potential utility of the BD MAX vaginal panel in the differential diagnosis of vaginitis. The authors indicated that future studies are required to establish the benefits regarding the application of this investigational test in a practical setting.

The BD MAX vaginal panel is capable of detecting several *Candida* species and TV in addition to diagnosing BV via a proprietary algorithm which performs a quantitative assessment of *G. vaginalis*, *Megasphaera type 1, A. vaginae, Lactobacillus spp*., and BVAB2. In a cross-sectional study by Gaydos et al. (2017) the BD MAX assay results were compared to reference methods for the diagnosis of BV (Nugent's and Amsel's criteria), *Candida* infection (culture), and trichomoniasis (wet mount and culture) in samples collected from 1,740 symptomatic women. BD MAX test sensitivity was 90.5% (95% CI 88.3-92.2%) and specificity was 85.8% (95% CI 83.0-88.3%) for BV. *Candida* group test sensitivity was 90.9% (95% CI 88.1-93.1%) and specificity was 94.1% (95% CI 92.6-95.4%), with lower sensitivity for *Candida glabrata* [75.9% (95% CI 57.9-87.8%)] but a high specificity [99.7% (95% CI 99.3-99.9%)]. BD MAX vaginal panel test sensitivity was 93.1% (95% CI 87.4-96.3%) and specificity was 99.3% (95% CI 98.7-99.6%) for the presence of TV. According to the authors, this investigational test appears to be a promising molecular assay for detection of vaginitis using molecular amplification of vaginal microbiome organisms, indicating a one-assay platform could potentially aid clinicians in

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diagnosing vaginitis. Research will be required to demonstrate performance and outcomes in various populations such as pregnant women, hypoestrogenic women, and asymptomatic women.

Clinical Practice Guidelines

American College of Obstetricians and Gynecologists (ACOG)

ACOG published a Clinical Management Guideline to describe the diagnosis and treatment of the common causes of vaginitis in nonpregnant women (2020). In the summary of recommendations, ACOG gives the following recommendations a Level A rating (based on good and consistent scientific evidence):

- Use of Amsel clinical criteria or Gram stain with Nugent scoring for the diagnosis of BV.
- NAAT for the diagnosis of TV.
- In a symptomatic patient, diagnosis of VVC requires one of the following two findings:
  - Spores, pseudohyphae, or hyphae on wet-mount microscopy; or
  - Positive vaginal fungal culture or commercial diagnostic test.

Level B recommendations (based on limited of inconsistent scientific evidence) include pap tests are not reliable for the diagnosis of vaginitis. Diagnostic confirmation is recommended for incidental findings of VVC, BV or TV on a Pap test.

British Association for Sexual Health and HIV (BASHH)

BASHH recommends the following diagnostic tests in women presenting with signs and symptoms of vaginal infection:

- For suspected VVC infection, microscopy examination of wet prep slide is recommended; culture is only recommended in cases of recurrent infection. (BASHH, 2019, updated 2021)
- For BV, use of Amsel's criteria and Gram stain with Hay/Ison or Nugent criteria is outlined. DNA probe tests are mentioned has having adequate performance. (BASHH, 2012)
- For diagnosis of trichomoniasis, NAATs are recommended as the test of choice, as they offer the highest sensitivity and are considered the gold standard for TV diagnosis. (BASHH, 2021, updated 2022)

Centers for Disease Control and Prevention (CDC)

Guidelines from the Centers for Disease Control and Prevention (2021) state: "Despite the availability of BV NAATs, traditional methods of BV diagnosis, including the Amsel criteria, Nugent score, and the Affirm VP III assay, remain useful for diagnosing symptomatic BV because of their lower cost and ability to provide a rapid diagnosis." For TV, the guidelines indicate that wet-mount microscopy has historically been the preferred diagnostic test for TV because it is inexpensive and can be performed at point-of-care, however sensitivity is low (44%-68%) compared with culture. NAATs detect more TV infections than wet-mount microscopy due to their high sensitivity. Regarding the use of PCR testing for diagnosis of uncomplicated VVC, the guidelines state: "The majority of PCR tests for yeast are not FDA cleared, and providers who use these tests should be familiar with the performance characteristics of the specific test used. Yeast culture, which can identify a broad group of pathogenic yeasts, remains the reference standard for diagnosis."

Infectious Diseases Society of America/American Society for Microbiology

The Infectious Diseases Society of America and the American Society for Microbiology released a joint guide (Miller et al., 2024) that contains the following recommendations for the diagnosis of vaginosis/vaginitis:

- Nucleic acid amplification tests are recommended for suspected diagnosis of TV infection due to the wide variation in sensitivity and ability to detect TV between observers using microscopy.
- For the diagnosis of BV, the use of Amsel's clinical criteria or scored Gram stain of vaginal discharge are preferred over probe hybridization or culture for only *G. vaginalis* due to the lower specificity of probe and culture testing for BV.
- For candidiasis diagnosis, wet prep, culture, or DNA probe are the recommended methods, with culture being preferred in cases of recurrent candidiasis.

International Union Against Sexually Transmitted Infections (IUSTI)/World Health Organisation (WHO) Guideline on the Management of Vaginal Discharge

The 2018 IUSTI/WHO guidelines (Sherrard et al.) indicate the following:

- The reference method for diagnosing BV is Gram-stained Microscopy. Nugent score using the Gram-stained vaginal smear is considered the gold standard for studies. Hay-Ison criteria are also based on Gram-stained smear findings.
- Clinical criteria for diagnosing BV (Amsel) includes the presence of three of the following:
  - Homogeneous grey-white discharge
  - pH of vaginal fluid > 4.5 (measured using narrow gauge pH paper)
  - Fishy odor (if not recognizable, use 10% KOH)
  - Clue cells present on wet mount microscopy (> 20% of all epithelial cells)

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- Although commercial molecular tests for BV such as BD MAX are available, the Guidelines Group recommends microscopy using Hay-Ison criteria as the best test for diagnosing BV (strength of recommendation: Grade 1, quality of evidence: Grade A).
- For diagnosis of VVC, the Guideline Group recommends microscopy as the current best test (strength of recommendation: Grade 1, quality of evidence: Grade B).
- The Guideline Group recommends the use of NAATs to diagnose TV (strength of recommendation: Grade 1, quality of evidence: Grade A).

United States Preventive Services Task Force (USPSTF)

The USPSTF (2020) published a recommendation statement that advises against screening for BV in pregnant women who do not have signs or symptoms of BV and who are not an increased risk for premature delivery (grade D). The task force recommends additional research to determine if BV screening for patients at risk for pre-term delivery is beneficial. These recommendations were based on supporting evidence from a systematic review and evidence synthesis including over 40 publications. (Kahwati et al., 2020)

U.S. Food and Drug Administration (FDA)

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

There are several commercial nucleic acid-based tests including both DNA probe tests and multiplex polymerase chain reaction (PCR) kits for genitourinary pathogen detection that have been cleared through the FDA 510(k) clearance process. More information regarding specific tests and FDA approval status may be found on the FDA website at: https://www.fda.gov/medical-devices/vitro-diagnostics/nucleic-acid-based-tests. (Accessed December 18, 2025)

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Policy History/Revision Information

Date	Summary of Changes
07/01/2025	**Applicable Codes** • Updated list of applicable CPT codes to reflect quarterly edits; added 0557U **Supporting Information** • Archived previous policy version UMR2025T0608K

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