Genitourinary Pathogen Nucleic Acid Detection Panel Testing

Policy Number: LABORATORY 029.2 T2
Effective Date: September 1, 2020

Instructions for Use

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Related Policies
None

Coverage Rationale

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

- Direct and amplified DNA probe testing for *Trichomoniasis vaginalis*
- Direct probe testing for *Candida sp*

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

- Amplified DNA probe testing for vulvovaginitis due to *Candida sp*
- 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

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

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

Required Clinical Information
Genitourinary Pathogen Nucleic Acid Detection Panel Testing
Medical notes documenting all of the following: • Diagnosis • History of illness, including date of onset, and physical exam findings • Specific tests being ordered (e.g., test requisition form)

Definitions

Sexually Transmitted Infection (STI): An STI is an infection that is spread by sexual contact. Infections include chlamydia, gonorrhea, human papillomavirus (HPV), herpes, syphilis, and human immunodeficiency virus (HIV). (American College of Obstetricians and Gynecologists, 2019)

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

Prior Authorization Requirements

Prior authorization is required in all sites of service.

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 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 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
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

CPT Code	Description
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

Description of Services

Bacterial Vaginosis (BV), *Trichomonas vaginalis (T. vaginalis)* and *Candida* species cause the highest number of cases of acute vulvovaginal symptoms that lead a woman to seek medical care. 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. (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. The most recent version of this test, Affirm VPIII, utilizes hybridization of specific organismal sequences to specific labeled DNA probes to detect *Candida* species, *Gardnerella vaginalis* (as a marker for BV), and *T. vaginalis*.

Clinical Evidence

DNA Probe Testing

DNA probe testing for *Trichomoniasis vaginalis* or *Candida sp* 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 bacterial vaginosis and amplified DNA probe tests for vulvovaginitis due to *Candida sp*.

DNA probe tests 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) 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 VIP 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 turns influences the clinical utility of the DNA probe tests.

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 does not currently recommend screening of asymptomatic pregnant women for bacterial vaginosis although workup of symptomatic women is recommended (USPSTF, 2008). 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, 2015)

Diagnosis of bacterial vaginosis 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 presence of clue cells on microscopy (CDC, 2015). These criteria are indicative of the microbiota changes associated with bacterial vaginosis which allow overgrowth of species such as *Gardnerella vaginalis*. The Gram stain is the gold-standard for BV diagnosis and evaluates the quantity of normal flora versus BV flora. Gram stains may be used in conjunction with Nugent's criteria to score the samples and categorize them as being normal flora (0-3), intermediate/mixed flora (4-6), or indicative of bacterial vaginosis (7-10) (Coleman and Gaydos, 2018).

Research indicates that this microscope-grounded clinical diagnosis of bacterial vaginosis is inconsistently reliable, in part because it relies upon a clinician's willingness, ability and skill to review slides at a microscope to identify cytologic characteristics of the disease and to apply the findings to clinical criteria. A study designed to evaluate agreement among observers reviewing Gram stains for a diagnosis of bacterial vaginosis found complete agreement among reviewers in 76.2 percent of cases (Mohanty et al., 2010). Another study used κ chance-corrected agreement statistics to compare the microscopic diagnosis of *Candida* and bacterial vaginosis on wet prep by blinded pairs of observers; the study found agreement was moderate (κ=0.45) for bacterial vaginosis and fair (κ=0.3) for candidiasis in a ranking system with possible outcomes of almost perfect, substantial, moderate, fair and poor agreement. (Whiteside et al., 2011)

While bacterial vaginosis is a condition that can be identified on Pap test, it is a diagnosis that is often missed. Conventional Pap smear techniques have higher diagnostic utility than liquid-based thin-layer prep (Takei et al., 2006), but due to low sensitivity and specificity, the CDC does not recommend the use of Pap smear for the diagnosis of bacterial vaginosis. Bacterial culture is also not recommended as it is nonspecific. (CDC, 2015)

Methods such as broad-range and quantitative polymerase chain reaction (PCR) have identified novel bacteria associated with BV while also providing more objective, quantitative measures of bacterial presence (Ravel et al., 2011). These tests have also enabled a greater understanding of the complexity of microflora alterations underlying bacterial vaginosis and provided more probative tools for developing improved diagnostic tests. A study using PCR to identify bacteria in women with bacterial vaginosis found *Gardnerella vaginalis* in 100% of women with bacterial vaginosis but also found the bacterium in 60% of women without this syndrome (Fredricks et al., 2005). A number of studies have been published describing the use of quantitative or semi-quantitative PCR methodologies for diagnosing BV (Sha et al., 2005; Menard et al., 2008). A unified clinical approach for using PCR technology to diagnose BV has not yet been established.

According to the CDC, the Gram stain remains the gold standard laboratory method. While other tests, such as the Affirm VP III, have been shown to have acceptable performance characteristics compared with the Gram stain, they have not become the gold standard. PCR tests have only been evaluated in research settings and have yet to show clinical utility. Additional validation is needed prior to the use of PCR for detection of BV. (CDC, 2015)

Trichomonas Vaginalis (T. vaginalis)

T. vaginalis 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)

T. vaginalis is considered a sexually transmitted disease, and concurrent treatment is important for the index case and all sexual partners to eradicate infection. Like BV, *T. vaginalis* is one of the most common infections following sexual assault. Due to the high rate of reinfection with *T. vaginalis*, the CDC recommends retesting for *T. vaginalis* infection within 3 months following initial treatment for all sexually active women. (CDC, 2015)

Successful treatment of *T. vaginalis* infection is important because it has been associated with infertility and adverse pregnancy outcomes. Further, because *T. vaginalis* has been associated with increased vaginal shedding of HIV, screening of all HIV-positive women entering care is recommended by the Centers for Disease Control and Prevention. *T. vaginalis* can also cause cervicitis, leading to vaginal discharge, and the CDC recommends women with cervicitis who are symptomatic for the infection should have additional testing if trichomonads are not identified by microscopy. (CDC, 2015)

Although the characteristic flagellated organisms can be visualized moving about on wet prep, the sensitivity and specificity for the diagnosis of *T. vaginalis* on wet prep is low compared to culture. In a study comparing diagnostic modalities for the diagnosis of *T. vaginalis*, wet mount detected 56% of infections and rapid test plus wet mount increased detection to 86% (Pattullo et al., 2008). And while culture is a reliable diagnostic modality, it takes as many as five days for results (Huppert, 2009), and is no longer the gold standard for *T. vaginalis* diagnosis since the advent of valid molecular diagnostic methods. (CDC, 2015)

APTIMA *T. vaginalis* is a nucleic acid amplification test that has been reported to be more sensitive than culture for the diagnosis of *T. vaginalis* (Nye et al., 2009). In a large, multi-center trial sponsored by Gen-Probe, APTIMA *T. vaginalis* sensitivity was found to be 100% in vaginal swab, endocervical swab, and liquid cytology cervical specimens. The test also had high sensitivity for urine specimens. Specificities for the various specimen sources ranged from 98.9% to 99.6% (Schwebke et al., 2011). Another Gen-Probe sponsored study reported a sensitivity and specificity of 100% when using an in-house second transcription-mediated amplification test with a different primer and probe set as a confirmatory test. (Andrea and Chapin, 2011)

Vulvovaginal Candidiasis (VVC)

In the United States, *Candida 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 patients with recurrent VVC, defined as 4 or more cases in 12 months. (CDC, 2015)

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 and thus may escape microscopic diagnosis (CDC, 2015). 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)

A limited number of studies have been performed using nucleic acid amplification as a diagnostic tool for VVC. There are reports of superiority of PCR to culture for the diagnosis of *Candida* (Xiang et al., 2007) including patient populations with recurrent VVC (Giraldo et al., 2000; Weissenbacher et al., 2009). While there is not a compelling case to be made that routine testing of vaginal samples by PCR is necessary for accurate diagnosis of VVC, this technique clearly has the potential to provide diagnostic information of at least comparable value to the most widely accepted gold standard method for identifying VVC (namely culture) including identification of clinically-relevant species and mixed infections.

Panel Testing for Multiple Genitourinary Pathogens

There is a lack of studies that demonstrate clinical utility of panel testing for multiple genitourinary pathogens. Each of the clinical presentations of these infections is different for the various pathogens and there are unique single tests available. Nucleic acid amplification testing has limitations when applied to organisms that potentially form part of the normal human flora (Bursle and Robson, 2016). In an evaluation of a PCR assay for BV, van der Veer and colleagues (2018) concluded that while the test was sensitive, positive results need to be interpreted with clinical symptoms due to asymptomatic vaginal dysbiosis.

While the clinical presentations and diagnostic criteria are different from the different 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 MAX vaginal panel, MDL BV panel, SureSwab, and NuSwab. All tests are designed to detect bacterial species whose presence or absence is informative in the diagnosis of BV, but differ somewhat in which indicator organisms were selected for the panel, as well as in sensitivity and specificity metrics.

Schwebke and colleagues (2018) analyzed the BD MAX vaginal panel compared to reference, for detection of BV, *Candida* spp., and *T. vaginalis*. 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 3 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.

BD MAX vaginal panel is capable of detecting several *Candida* species and *T. vaginalis* in addition to diagnosing bacterial vaginosis 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 bacterial vaginosis (Nugent's and Amsel's criteria), *Candida* infection (culture), and trichomoniasis (wet mount and culture) for 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 bacterial vaginosis. 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 *T. vaginalis*. 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 diagnosing vaginitis. Research will be required to demonstrate performance and outcomes in various populations such as pregnant women, hypoestrogenic women, and asymptomatic women.

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 *T. vaginalis*. 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, vaginal specimens were collected for DNA probe analysis by Affirm VPIII. The patients 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 4 cases of *Candida*, 21 cases of BV, and 3 cases of mixed BV and *Candida*. Eight of twenty-eight women complaining of symptoms not resolved after the clinic visit represented missed cases of BV (Lowe et al., 2009). This study highlights that Affirm VPIII has the potential to decrease the number of repeat patient visits to establish a definitive diagnosis. Study limitations include its observational nature and small subgroup size for *trichomoniasis vaginalis*.

Professional Societies and Other Guidelines

American College of Obstetricians and Gynecologists (ACOG)

ACOG published a recent Clinical Management Guideline to describe the diagnosis and treatment of the common causes of vaginitis in nonpregnant women (ACOG 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
- Nucleic acid amplification testing (NAAT) for the diagnosis of trichomoniasis
- In a symptomatic patient, diagnosis of VVC requires one of the following two findings: 1) spores, pseudohyphae, or hyphae on wet-mount microscopy or 2) 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

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., 2018) that contains the following recommendations for the diagnosis of vaginosis/vaginitis:

- Nucleic acid amplification tests are recommended for suspected diagnosis of *T. vaginalis* infection due to the wide variation in sensitivity and ability to detect *T. vaginalis* between observers using microscopy.
- For the diagnosis of bacterial vaginosis, 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.

Centers for Disease Control and Prevention (CDC)

The CDC recommends the following diagnostic modalities for the treatment of bacterial vaginosis, *Trichomonas vaginalis* and *Candida* in the Sexually Transmitted Treatment Guidelines published in 2015 (CDC, 2015):

- For the diagnosis of bacterial vaginosis, the following tests are recommended: Amsel's clinical criteria or Gram stain. While DNA probe tests have been shown to have acceptable performance characteristics compared with Gram stain, the Gram stain remains the gold standard laboratory method. Other enzymatic activity tests, such as the proline aminopeptidase card test, are not recommended due to low sensitivity and specificity. Culture is not recommended and the Pap test is not useful for this purpose.
- For the diagnosis of *Trichomonas vaginalis* in women, the following tests are recommended: wet prep microscopy, DNA probe testing, rapid antigen tests, nucleic acid amplification tests, and culture. Due to its low sensitivity for detecting *T. vaginalis* in vaginal specimens, it is recommended that this method be used in conjunction with a highly sensitive test, such as nucleic acid amplification.
- For the diagnosis of *Candida,* a diagnosis can be made when wet prep, Gram stain, culture or other test is positive for a yeast species.

United State Preventive Services Task Force (USPSTF)

The USPSTF recommends against screening for bacterial vaginosis in pregnant women who are not at increased risk for preterm delivery. Additionally, it states that there is currently insufficient evidence to assess the benefits and risks of screening for bacterial vaginosis in pregnant women who are at risk for preterm delivery. (USPSTF 2008; USPSTF 2019)

British Association for Sexual Health and HIV

The British Association for Sexual Health and HIV recommends the following diagnostic tests in women presenting with signs and symptoms of vaginal infection. (British Association for Sexual Health and HIV, 2019; Sherrard et al., 2014)

- For suspected yeast infection, microscopy examination of wet prep slide is recommended; culture is only recommended in cases of recurrent infection.
- For diagnosis of trichomoniasis, nucleic acid amplification tests are recommended over microscopy or culture as it has higher sensitivity and is becoming the gold standard for *T. vaginalis* diagnosis.

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 multiplex polymerase chain reaction (PCR) kits that have been cleared through the FDA 510(k) clearance process. For 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 January 8, 2020)

References

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [*2020T0608A*]

Achkar JM, Fries BC. Candida infections of the genitourinary tract. Clin Microbiol Rev. 2010 Apr;23(2):253-73.

American College of Obstetricians and Gynecologists (ACOG). Chlamydia, Gonorrhea, and Syphilis. Frequently Asked Questions. FAQ071. February 2019. Available at: https://www.acog.org/Patients/FAQs/Chlamydia-Gonorrhea-and-Syphilis. Accessed January 14, 2020.

American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 215. Vaginitis in nonpregnant patients. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2020;135:e1-17.

Allsworth JE, Peipert JF. Prevalence of bacterial vaginosis: 2001-2004 National Health and Nutrition Examination Survey Data. Obstetrics & Gynecology. 2007;109(1):114-120.

Andrea SB, Chapin KC. Comparison of Aptima Trichomonas vaginalis transcription-mediated amplification assay and BD affirm VPIII for detection of T. vaginalis in symptomatic women: performance parameters and epidemiological implications. J Clin Microbiol. 2011 Mar;49(3):866-9.

British Association for Sexual Health and HIV national guideline for the management of vulvovaginal candidiasis. 2019. Available at: https://www.bashhguidelines.org/media/1223/vvc-2019.pdf. Accessed December 6, 2019.

Bursle E, Robson J. Non-culture methods for detecting infection. Aust Prescr. 2016 Oct;39(5):171-175.

Centers for Disease Control and Prevention (CDC). Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR Recomm Rep 2015;64(No. RR-3): 1-137.

Coleman JS, Gaydos CA. Molecular Diagnosis of Bacterial Vaginosis: an Update. J Clin Microbiol. 2018 Aug 27;56(9).

Ferris DG, Hendrich J, Payne PM, et al. Office laboratory diagnosis of vaginitis. Clinician-performed tests compared with a rapid nucleic acid hybridization test. J Fam Pract. 1995 Dec;41(6):575-81.

Ferris DG, Nyirjesy P, Sobel JD, et al. Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis. Obstet Gynecol. 2002 Mar;99(3):419-25.

Fredricks DN, Fiedler TL, Marrazzo JM. Molecular identification of bacteria associated with bacterial vaginosis. N Engl J Med. 2005 Nov 3;353(18):1899-911.

Gaydos CA, Beqaj S, Schwebke JR, et al. Clinical validation of a test for the diagnosis of vaginitis. Obstet Gynecol. 2017 Jul;130(1):181-189.

Giraldo P, von Nowaskonski A, Gomes FA, et al. Vaginal colonization by Candida in asymptomatic women with and without a history of recurrent vulvovaginal candidiasis. Obstet Gynecol. 2000 Mar;95(3):413-6.

Huppert JS. Trichomoniasis in teens: an update. Curr Opin Obstet Gynecol. 2009 Oct;21(5):371-8.

Jones, A. Bacterial vaginosis: A review of treatment, recurrence, and disparities. The Journal for Nurse Practitioners. 2019.

Koumans EH, Sternberg M, Bruce C, et al. The prevalence of bacterial vaginosis in the United States, 2001-2004; associations with symptoms, sexual behaviors, and reproductive health. Sex Transm Dis. 2007 Nov;34(11):864-9.

Levi AW, Harigopal M, Hui P, et al. Comparison of Affirm VPIII and Papanicolaou tests in the detection of infectious vaginitis. *Am J Clin Pathol*. 2011;135:442-447.

Lowe NK, Neal JL, Ryan-Wenger NA. Accuracy of the clinical diagnosis of vaginitis compared with a DNA probe laboratory standard. Obstet Gynecol. 2009 Jan;113(1):89-95.

Menard JP, Fenollar F, Henry M, et al. Molecular quantification of Gardnerella vaginalis and Atopobium vaginae loads to predict bacterial vaginosis. Clin Infect Dis. 2008 Jul 1;47(1):33-43.

Miller JM, Binnicker MJ, Campbell S, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. 2018 Aug 31;67(6):e1-e94.

Mohanty S, Sood S, Kapil A, et al. Interobserver variation in the interpretation of Nugent scoring method for diagnosis of bacterial vaginosis.Indian J Med Res. 2010 Jan;131:88-91.

Nye MB, Schwebke JR, Body BA. Comparison of APTIMA Trichomonas vaginalis transcription-mediated amplification to wet mount microscopy, culture, and polymerase chain reaction for diagnosis of trichomoniasis in men and women. Am J Obstet Gynecol. 2009 Feb;200(2):188.e1-7.

Paavonen J, Brunham RC. Bacterial vaginosis and desquamative inflammatory vaginitis. N Engl J Med. 2018 Dec 6;379(23):2246-2254.

Pattullo L, Griffeth S, Ding L, et al. Stepwise diagnosis of Trichomonas vaginalis infection in adolescent women. J Clin Microbiol. 2009 Jan;47(1):59-63.

Ravel J, Gajer P, Abdo Z, et al. Vaginal microbiome of reproductive-age women. Proc Natl Acad Sci U S A. 2011 Mar 15;108 Suppl 1:4680-7.

Schwebke JR, Gaydos CA, Nyirjesy P, et al. Diagnostic performance of a molecular test versus clinician assessment of vaginitis. J Clin Microbiol. 2018 May 25;56(6).

Schwebke JR, Hobbs MM, Taylor SN, et al. Molecular testing for Trichomonas vaginalis in women: results from a prospective U.S. clinical trial. J Clin Microbiol. 2011 Dec;49(12):4106-11.

Schwiertz A, Taras D, Rusch K, et al. Throwing the dice for the diagnosis of vaginal complaints? Ann Clin Microbiol Antimicrob. 2006 Feb 17;5:4.

Sha BE, Chen HY, Wang QJ, et al. Utility of Amsel criteria, Nugent score, and quantitative PCR for Gardnerella vaginalis, Mycoplasma hominis, and Lactobacillus spp. for diagnosis of bacterial vaginosis in human immunodeficiency virus-infected women. J Clin Microbiol. 2005 Sep;43(9):4607-12.

Sherrard J, Ison C, Moody J, et al. United Kingdom National guideline on the management of Trichomonas vaginalis 2014. Int J STD AIDS. 2014 Jul;25(8):541-9.

Sobel JD. Vulvovaginal candidosis. Lancet. 2007 Jun 9;369(9577):1961-71.

Takei H, Ruiz B, Hicks J. Cervicovaginal flora. Comparison of conventional pap smears and a liquid-based thin-layer preparation. Am J Clin Pathol. 2006 Jun;125(6):855-9.

U.S. Preventive Services Task Force. Screening for bacterial vaginosis in pregnancy to prevent preterm delivery: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008 Feb 5;148(3):214-9

U.S. Preventive Services Task Force (USPSTF). Screening for bacterial vaginosis in pregnancy to prevent preterm delivery: Draft recommendation statement. 2019. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/bacterial-vaginosis-in-pregnant-adolescents-and-women-to-prevent-preterm-delivery-screening. Accessed December 5, 2019.

van der Veer C, van Houdt R, van Dam A, et al. Accuracy of a commercial multiplex PCR for the diagnosis of bacterial vaginosis. J Med Microbiol. 2018 Sep;67(9):1265-1270.

Weissenbacher T, Witkin SS, Ledger WJ, et al. Relationship between clinical diagnosis of recurrent vulvovaginal candidiasis and detection of Candida species by culture and polymerase chain reaction. Arch Gynecol Obstet. 2009 Feb;279(2):125-9.

Whiteside JL, Small TA, MacKenzie TA, et al. Interobserver reliability of microscopic assessment of saline-prepared vaginal fluid. J Low Genit Tract Dis. 2011 Apr;15(2):120-3.

Witt A, Petricevic L, Kaufmann U, et al. DNA hybridization test: rapid diagnostic tool for excluding bacterial vaginosis in pregnant women with symptoms suggestive of infection. J Clin Microbiol. 2002 Aug;40(8):3057-9.

Xiang H, Xiong L, Liu X, et al. Rapid simultaneous detection and identification of six species Candida using polymerase chain reaction and reverse line hybridization assay. J Microbiol Methods. 2007 May;69(2):282-7.

Policy History/Revision Information

Date	Summary of Changes

09/01/2020	**Template Update**
	• Reformatted policy; transferred content to new template
	• Removed and replaced section titled *Conditions of Coverage* with *Prior Authorization Requirements*
	  ○ Simplified and relocated language pertaining to prior authorization guidelines
	  ○ Removed language addressing benefit type and referral requirements (refer to the member specific benefit plan document)
	• Replaced references to “precertification” with “prior authorization”
	Supporting Information
	• Archived previous policy version LABORATORY 029.1 T2

Instructions for Use

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.