Diagnosis of Vaginitis including Multi-target PCR Testing

Policy Number: AHS – M2057 – Diagnosis of Vaginitis including Multi-target PCR Testing	Prior Policy Name and Number, as applicable:
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I. Policy Description

Vaginitis is defined as inflammation of the vagina with symptoms of discharge, itching, and discomfort often due to a disruption of the vaginal microflora. The most common infections are bacterial vaginosis, *Candida* vulvovaginitis, and trichomoniasis (Sobel, 1999). Other causes include vaginal atrophy in postmenopausal women, cervicitis, foreign body, irritants, and allergens (Sobel, 2020a).

Bacterial vaginosis (BV) is characterized by a shift in microbial species from the normally dominant hydrogen-peroxide producing *Lactobacillus* species to *Gardnerella vaginalis* and anaerobic commensals (Eschenbach et al., 1989; Hill, 1993; Lamont et al., 2011; Ling et al., 2010; Sobel, 2020b).

Vulvovaginal candidiasis (VVC) is usually caused by *Candida albicans* but can occasionally be caused by other *Candida* species (CDC, 2021d). It is the second most common cause of vaginitis symptoms (after BV) and accounts for approximately one-third of vaginitis cases (Sobel, 2020c; Workowski & Bolan, 2015).

Trichomoniasis is caused by the flagellated protozoan *Trichomonas vaginalis*, which principally infects the squamous epithelium in the urogenital tract: vagina, urethra, and paraurethral glands (Kissinger, 2015; Sobel & Mitchell, 2020).

II. Related Policies

Policy Number	Policy Title
AHS-G2157	Diagnostic Testing of Common Sexually Transmitted Infections
AHS-G2002	Cervical Cancer Screening

AHS-M2097	Identification of Microorganisms Using Nucleic Acid Probes
AHS-G2149	Pathogen Panel Testing

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

1) Testing of pH, testing for the presence of amines, saline wet mount, hydrogen peroxide (KOH) wet mount and microscopic examination of vaginal fluids **MEETS COVERAGE CRITERIA** in individuals with symptoms of vaginitis.

2) Direct Probe DNA-based identification of *Gardnerella*, *Trichomonas*, and *Candida* **MEETS COVERAGE CRITERIA** in individuals with symptoms of vaginitis.

3) Vaginal cultures for *Candida* species **MEET COVERAGE CRITERIA** for the diagnosis of vulvovaginal candidiasis in individuals with clinical signs and symptoms of vaginitis and negative findings on wet-mount preparations and a normal pH test.

4) Measurement of sialidase activity in vaginal fluid **MEETS COVERAGE CRITERIA** for the diagnosis of bacterial vaginosis in individuals with symptoms of vaginitis.

5) Nucleic Acid Amplification Test (NAAT) or Polymerase Chain Reaction (PCR)-based identification of *Trichomonas vaginalis* **MEETS COVERAGE CRITERIA** in individuals with symptoms of vaginitis.

6) Screening for *Trichomonas* **MEETS COVERAGE CRITERIA** for individuals with risk factors including: new or multiple partners; history of sexually transmitted diseases (STDs), especially HIV; exchange of sex for payment; incarceration, or injection drug use.

7) Polymerase Chain Reaction (PCR) based identification of *Candida* **MEETS COVERAGE CRITERIA** for individuals with complicated vulvovaginal candidiasis (VVC) to confirm clinical diagnosis and identify non-*albicans Candida*.

8) Nucleic Acid Amplification Test (NAAT), polymerase chain reaction (PCR) testing, and Multitarget PCR testing, when limited to known pathogenic species, **MEETS COVERAGE CRITERIA** for the diagnosis of bacterial vaginosis**.**

9) Screening for trichomoniasis and bacterial vaginosis **DOES NOT MEET COVERAGE CRITERIA** in asymptomatic individuals, including asymptomatic pregnant individuals at average or high risk for premature labor.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

10) Rapid identification of *Trichomonas* by enzyme immunoassay **DOES NOT MEET COVERAGE CRITERIA** in individuals with symptoms of vaginitis.

11) Using molecular-based panel testing, including, but not limited to testing such as SmartJane™, to test for microorganisms involved in vaginal flora imbalance and/or infertility **DOES NOT MEET COVERAGE CRITERIA**.

12) All other tests for vaginitis not addressed above **DO NOT MEET COVERAGE CRITERIA**.

IV. Table of Terminology

Term	Definition
AAFP	American Academy of Family Physicians
ACOG	American College of Obstetrics and Gynaecology
ASM	American Society for Microbiology
AV	Aerobic vaginitis
BV	Bacterial vaginosis
BVAB	BV associated bacteria
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare and Medicaid
DNA	Deoxyribose nucleic acid
HIV	Human Immunodeficiency Virus
IDSA	Infectious Diseases Society of America
LDTs	Laboratory developed tests
NAAT	Nucleic acid amplification test
OADS	Office of the Associate Director for Science
PCR	Polymerase chain reaction
PMNs	Polymorphonuclear cells
RTPCR	Real-time polymerase chain reaction
SOGC	Society Of Obstetricians and Gynaecologists of Canada
STDs	Sexually transmitted diseases
TMA	Transcription Mediated Amplification
TV	Trichomonas vaginalis
USPSTF	U.S. Preventive Services Task Force
VVC	Vulvovaginal candidiasis

V. Scientific Background

Vaginitis is characterized by several symptoms including odor, itching, abnormal vaginal discharge, burning and irritation; this inflammatory ailment is considered the most common gynecologic diagnosis in primary care as most women experience vaginitis at least once in their

lives (Paladine & Desai, 2018). A diagnosis of vaginitis can be given based on a combination of symptoms, physical examination, and office or laboratory-based testing methods.

The squamous epithelium of the vagina in premenopausal women is rich in glycogen, a substrate for lactobacilli, which create an acidic vaginal environment (pH 4.0 to 4.5). This acidity helps maintain the normal vaginal flora and inhibits growth of pathogenic organisms. Disruption of the normal ecosystem by menstrual cycle, sexual activity, contraceptive, pregnancy, foreign bodies, estrogen level, sexually transmitted diseases, and use of hygienic products or antibiotics can lead to development of vaginitis. Bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), and trichomoniasis are the three most common infections responsible for vaginitis. Other causes include: vaginal atrophy in postmenopausal women, cervicitis, foreign body, irritants and allergens (Sobel, 2020a).

Bacterial vaginosis is caused by an imbalance of naturally occurring vaginal bacteria, characterized by both a change in the most common type of bacteria present, along with an increase in the total number of bacteria present. Normal vaginal microbiota is dominated by the species *Lactobacilli*, which are known to produce hydrogen peroxide and lactic acid, which help to keep the acidic vaginal environment below pH 4.5 (Jones, 2019; Kairys & Garg, 2020). Though the origin of vaginal bacterial infections is still unclear, it is believed that most of such infections are the result of another bacteria, *Gardnerella vaginalis*, creating a biofilm which allows opportunistic bacteria to grow within the vagina, causing a decrease in the *Lactobacilli* and subsequent disruption of the pH of the system. An entire host of etiologic organisms have been identified as possible instigators and exacerbators, including *Atopobium vaginae*, *Megasphaera* phylotype 1 and 2, *Leptotrichia aminionii*, *Mobiluncus spp*, *Prevotella spp*, *Mycoplasma hominis*, *Bacteroides spp*, *Sneathia*, and BV-associated bacteria (BVAB)1, 2, and 3, though as aforementioned the causative mechanism and the interaction between these species are still uncertain (Jones, 2019).

Laboratory documentation of the etiology of vaginitis is important before initiating therapy, given the nonspecific nature and considerable overlap of the symptoms (Anderson, Klink, & Cohrssen, 2004; Ellis, Lerch, & Whitcomb, 2001; Landers, Wiesenfeld, Heine, Krohn, & Hillier, 2004). Diagnostic testing enables targeted treatment, increases therapeutic compliance, and increases the likelihood of partner notification (Sobel, 2020a; Workowski & Bolan, 2015).

Measurement of vaginal pH is the primary initial finding that drives the diagnostic. The pH of the normal vaginal secretions in premenopausal women with relatively high estrogen levels is 4.0 to 4.5. The pH of normal vaginal secretions in premenarchal and postmenopausal women in whom estrogen levels are low is ≥4.7. An elevated pH in a premenopausal woman suggests infections, such as BV (pH>4.5) or trichomoniasis (pH 5 to 6) and helps to exclude *Candida* vulvovaginitis (pH 4 to 4.5). Vaginal pH may also be altered by lubricating gels, semen, douches, intravaginal medications and in pregnant women, leakage of amniotic fluid (Anderson et al., 2004; Sobel, 2020a).

Analytical Validity

Microscopic examination of normal vaginal discharge reveals a predominance of squamous epithelial cells, rare polymorphonuclear leukocytes (PMNs), and *Lactobacillus* species. The primary goal of the examination is to look for candidal buds or hyphae, motile trichomonads, epithelial cells studded with adherent coccobacilli (clue cells), and increased numbers of PMNs (Sobel, 2020a). The microscopic evaluation of BV is usually based on Amsel criteria (Amsel et al., 1983). Amsel criteria state that the presence of at least three out of the following four criteria are indicative of a BV diagnosis: increased homogeneous thin vaginal discharge, pH secretion > 4.5, amine odor when potassium hydroxide 10% solution is added to a vaginal secretion sample, and the presence of clue cells in wet preparations (Amsel et al., 1983). If clinical criteria are used to define infection, then reported sensitivity may range from 62 to 100 percent (Spiegel, 1991). Using Gram's stain as the standard for diagnosing BV, the sensitivity of Amsel criteria for diagnosis of BV is over 90 percent and specificity is 77 percent (Landers et al., 2004). The Nugent score is also available as a Gram staining scoring system to diagnose BV based on vaginal swab samples (Amegashie et al., 2017). Because BV represents complex changes in the vaginal flora, vaginal culture has **no** role in diagnosis. If microscopy is not available, commercial diagnostic testing methods (eg, rapid antigen and nucleic acid amplification tests) are used for confirming the clinical suspicion of BV. Polymerase chain reaction (PCR)-based assays to quantify BV-associated bacteria (Cartwright et al., 2012; Menard, Fenollar, Henry, Bretelle, & Raoult, 2008) have good sensitivity and specificity compared with standard clinical tests (Dumonceaux et al., 2009; Menard et al., 2010). However, they are expensive and of limited utility (Sobel, 2020b).

Trichomoniasis can be diagnosed by the presence of motile trichomonads on wet mount, but it is identified in only 60 to 70 percent of culture-confirmed cases. Culture on Diamond's medium was considered the gold standard method for diagnosing a *T. vaginalis* infection (Workowski & Bolan, 2015); however, nucleic acid amplification tests (Baron et al., 2013) have become the accepted gold standard for the diagnosis of *T. vaginalis*. One study found the sensitivities for *T. vaginalis* using wet mount, culture, rapid antigen testing, and transcription-mediated amplification testing were 65, 96, 90, and 98 percent, respectively (Huppert et al., 2007). Coexistence of *T. vaginalis* and BV pathogens is common, with coinfection rates of 60 to 80 percent (Sobel & Mitchell, 2020; Sobel, Subramanian, Foxman, Fairfax, & Gygax, 2013).

Microscopy is negative in up to 50 percent of patients with culture-confirmed VVC (Sobel, 1985). Since there are no reliable point of care tests for *Candida* available in the United States (Abbott, 1995; Chatwani et al., 2007; Dan, Leshem, & Yeshaya, 2010; Hopwood, Evans, & Carney, 1985; Marot-Leblond et al., 2009; Matsui et al., 2009), culture must be obtained. PCR methods have high sensitivity and specificity and a shorter turn-around time than culture (Diba, Namaki, Ayatolahi, & Hanifian, 2012; Mahmoudi Rad, Zafarghandi, Amel Zabihi, Tavallaee, & Mirdamadi, 2012; Tabrizi, Pirotta, Rudland, & Garland, 2006; Weissenbacher et al., 2009), but they are costly and offer no proven benefit over culture in symptomatic women (Sobel, 2020c).

Lynch et al. (2019) collected vaginal swabs from 93 women in a cross-sectional study; results from microscopy were compared to two molecular approaches (a qPCR assay with a BV interpretive algorithm and a microbiome profiling test of the 16S rRNA gene produced by Illumina) (Lynch et al., 2019). Results show that “Microscopy plus BV Nugent score had 76% overall agreement with the qPCR plus BV interpretive algorithm method”; further, “Microscopic

identification of *Candida* versus that by qPCR had 94% agreement (9 positive, 78 negative) (Lynch et al., 2019)." The qPCR assays gave additional information regarding the types of bacteria present, and the 16S microbiome analysis identified differentiating patterns between BV, aerobic vaginitis (AV), and *Lactobacillus* type infections.

Cartwright, Pherson, Harris, Clancey, and Nye (2018) have published data regarding the clinical validity of a PCR-based assay for the detection of BV. This multicenter study included 1579 patients and compared PCR results to samples realized by both the Nugent gram stain and a clinical evaluation using Amsel criteria. Next-generation sequencing was used to confirm differing results. After the resolution of discordant test results using next-generation sequencing, the BV-PCR assay reported a sensitivity of 98.7%, a specificity of 95.9%, a positive predictive value of 92.9% and a negative predictive value of 96.9% (Cartwright et al., 2018). These results show that this PCR-based assay can diagnose BV in symptomatic women efficiently.

Anand et al. (2020) investigated the accuracy of Papanicolaou smear to diagnose bacterial vaginosis infection in women with women with clinically evident genital infection using the Nugent score on Gram-stained smear as the gold standard. In a prospective blinded cross-sectional study of 254 nonpregnant women between the ages of 30 and 50 conducted between August 2016 and August 2018, the researchers found that using the Nugent score for diagnosing BV as the gold standard, the Pap smears showed sensitivity and specificity of 70.9% (CI: 61.5% - 79.2%) and 56.8% (CI: 48.2% - 65.2%), respectively. Moreover, they found that the positive percent value was 56.5% (CI: 47.8% - 64.9%), while the negative percent value was 71.2% (CI: 61.8% - 79.4%). These results indicated to the authors that though Pap smears are generally reserved for cervical cancer, the "Pap smear may serve as a means of diagnosing BV [bacterial vaginosis] infection in resource-constrained countries like India" (Anand et al., 2020).

Clinical Utility and Validity

As previously stated, microscopy, rather than bacterial culture, is the standard of care for diagnosing BV, and commercially available tests are available in the absence of microscopy but are not widely used. A study of 176 women using the Affirm VP III test (a DNA hybridization probe test that identifies high concentrations of *G. vaginalis*) reported comparable results to wet mount examination with no false positives and only three false negatives for *T. vaginalis*, and three false positives and four false negatives for *G. vaginalis* (Briselden & Hillier, 1994). This test "takes less than one hour to perform and is the best option when findings on physical examination suggest BV… but microscopy cannot be performed to look for clue cells (Sobel, 2020b)."

The OSOM BVBlue chromogenic diagnostic point-of-care test is a CLIA-waived test with a reported 10 minute read time. One study of 173 pregnant women reported a sensitivity and specificity of 94% and 96% respectively, as compared to Gram stain score (Sumeksri, Koprasert, & Panichkul, 2005). These results were comparable to the previously reported values of 91.7% sensitivity and 97.8% specificity in an earlier, smaller study of non-menstruating women (n=57) (Myziuk, Romanowski, & Johnson, 2003). A larger study (n=288 women) reported a sensitivity of 88% and specificity of 91% as compared to the Amstel criteria. The authors of this report concluded that women who "are not in settings where the conventional diagnostic methods are

either practical or possible… would greatly benefit from access to rapid and reliable point-of-care tests to improve the diagnosis and management of BV (Bradshaw et al., 2005)."

The FDA approved the use of the BD MAX™ Vaginal Panel as "an automated qualitative *in vitro* diagnostic test for the direct detection of DNA targets from bacteria associated with BV (qualitative results reported based on detection and quantitation of targeted organism markers), *Candida* species associated with vulvovaginal candidiasis, and *Trichomonas vaginalis* from vaginal swabs in patients who are symptomatic for vaginitis/vaginosis. The test utilizes real-time PCR for the amplification of specific DNA targets and utilizes fluorogenic target-specific hybridization probes to detect and differentiate DNA (FDA, 2016)." A 2017 cross-sectional, multi-site study into the clinical validation of this system (n=1740 symptomatic women) reported a sensitivity and specificity of 90.9% and 94.1%, respectively for the *Candida* group and 90.5% sensitivity and 85.8% specificity for BV. For *C. glabrata* specifically, the assay had only 75.9% sensitivity but 99.7% specificity. For trichomoniasis, the sensitivity and specificity were 93.1% and 99.3%, respectively (Gaydos et al., 2017). These researchers also compared the results of this test to clinician assessment. Again, to qualify for the study, the women must have at least one symptom of BV. Using Amsel's criteria, the investigational test sensitivity was 92.7% as compared to the 75.6% sensitivity of the clinician assessment. The authors conclude, "The investigational test showed significantly higher sensitivity for detecting vaginitis, involving more than one cause, than did clinician diagnosis. Taken together, these results suggest that a molecular investigational test can facilitate accurate detection of vaginitis (Schwebke et al., 2018)." It should be noted, however, that these studies only included symptomatic women, and, therefore, the possible clinical nonspecificity (i.e., instances where an asymptomatic woman would test positive) is not addressed. Sherrard (2019) compared BV, candidiasis, and trichomoniasis diagnostic results from the BD MAX Vaginal Panel to a current test used in a UK specialist sexual health service center. The authors reported that the BD MAX Vaginal Panel had a sensitivity of 86.4% and specificity of 86.0% for *Candida* species, and a sensitivity of 94.4% and specificity of 79% for BV; the specificity for BV was lower in this study than what has been previously reported (Sherrard, 2019).

SureSwab® (Quest Diagnostics, Inc.) is a multi-target PCR test using RT-PCR to screen for a number of microorganisms involved in vaginal flora imbalances, including *B. vaginalis, T. vaginalis, C. albicans, C. glabrata, C. tropicalis,* and *C. parapsilosis*, from a vaginal swab. The swab can be collected either by a physician or the patient (Quest, 2019a). Similarly, Quest Diagnostics also offers the SureSwab® Vaginosis/Vaginitis Plus test, which tests for the presence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in addition to the microorganisms of the SureSwab® test (Quest, 2019b). The test is based on the unique set of primers synthesized by a CDC research team to identify *Candida* that purports to diagnose vulvovaginal candidiasis while ruling out other genital infections (CDC, 2016). The CDC research group, led by Dr. C.J. Morrison, developed the DNA probes to identify medically important *Candida* species by the internal transcribed spacer 2 region of ribosomal DNA. The specific hybridization was measured by a sample-to-background ratio of 58.7, 53.2, 46.9, 59.9, and 54.7 for *C. albicans, C. tropicalis, C. glabrata, C. parapsilosis,* and *C. krusei*, respectively. The negative control sample-to-background ratio was 0.9 (Das, Brown, Kellar, Holloway, & Morrison, 2006).

The OSOM *Trichomonas vaginalis* (TV) Rapid Test by Sekisui Diagnostics is "an antigen-detection test using immunochromatographic capillary flow dipstick technology that can be performed at the point of care (CDC, 2015b)." The diagnostic accuracy of the OSOM TV Rapid assay was tested against the common laboratory-based Anyplex II STI-7 Detection in a South African cross-sectional study; all irregular results were further tested with the Fast Track Diagnostics (FTD) STD9 assay (Garrett et al., 2019). Vaginal swabs from 247 women were tested for this study. "The sensitivity and specificity of OSOM TV were 75.0% (45.0-100) and 100% (100-100)", respectively, showing a very high specificity and lower sensitivity (Garrett et al., 2019).

The AMPLISwab™ by MedLabs is a comprehensive test created to assess the different organisms responsible for a variety of female genital tract infections, including causative pathogens for cervicitis, nongonococcal urethritis, pelvic inflammatory disease and infertility, sexually transmitted infections, and vaginitis (e.g., bacterial vaginosis, candidiasis and trichomoniasis). The test requires one swab to test for 23 total organisms, broken down into four categories (7 yeast, 12 bacteria and 1 reference bacteria, 1 parasite, and 2 types of herpes viruses), employing testing methodologies such as automated DNA/RNA extraction, transcription mediated amplification (TMA), and real-time polymerase chain reaction (RT-PCR) for the quantification of select organisms implicated in bacterial vaginosis (MedLabs, 2015).

The multiplex PCR assay SmartJane™ measures a specimen's vaginal flora (such as *Lactobacillus iners* or *Treponema pallidum*). The test proposes that the results can provide a health snapshot of the environment tested based on the levels of microorganisms detected. The procedure for the test requires the user to self-sample by collecting a vaginal swab and sending the sample back to Ubiome where it is analyzed. The labs use Precision Sequencing technology to extract DNA from the microorganisms in the sample and Illumina Next-Generation to sequence the targeted genes. Then, phylogenetic algorithms are used to analyze and organize the DNA from those microorganisms. Finally, a clinical report detailing the levels of the targeted microorganisms is sent to the user and medical provider (Ubiome, 2018). The report contains measurements of its targeted microorganisms, informing the patient whether those measurements are within the normal reference ranges for certain conditions, and whether certain high danger pathogens are present. The manufacturers state that on average SmartJane™ has a sensitivity and specificity for the species of microorganism of 99.4% and 100.0%, respectively. SmartJane™ tests for 19 different HPV strains and common pathological agents involved in sexually transmitted infections in addition to more than 20 different microorganisms involved in BV, including *G. vaginalis* (Ubiome, 2017).

Even though studies have shown that PCR methods have a higher specificity and sensitivity than culture and shorter turn-around time in identifying *Candida* (Diba et al., 2012; Mahmoudi Rad et al., 2012; Tabrizi et al., 2006; Weissenbacher et al., 2009), their use may be adding to clinical nonspecificity. Tabrizi et al. (2006) reported that PCR "detected four additional *Candida albicans*, three *Candida parapsilosis* and one *Candida tropicalis* when compared with culture. All but one case additionally detected by PCR were found in patients with no VVC symptoms (Tabrizi et al., 2006)." These data support the earlier findings by Giraldo et al. (2000) where, unlike culture testing, "*Candida* was identified by PCR in a similar proportion of patients with

previous recurrent vulvovaginal candidiasis (30%) and in controls (28.8%).” Taken together, these studies indicate that, even though PCR is more sensitive than culture, it may be identifying cases of *Candida* in asymptomatic women that are clinically irrelevant.

VI. Guidelines and Recommendations

Centers for Disease Control and Prevention (CDC)

The CDC published updated guidelines for diseases characterized by vulvovaginal itching, burning, irritation, odor or discharge in their Sexually Transmitted Infections Treatment Guidelines, 2021 (CDC, 2021b). These guidelines state that “obtaining a medical history alone has been reported to be insufficient for accurate diagnosis of vaginitis and can lead to inappropriate administration of medication…. Therefore, a careful history, examination, and laboratory testing to determine the etiology of any vaginal symptoms are warranted. Information regarding sexual behaviors and practices, sex of sex partners, menses, vaginal hygiene practices (e.g., douching), and self-treatment with oral and intravaginal medications or other products should be elicited.”

The CDC notes that “in the clinician’s office, the cause of vaginal symptoms can often be determined by pH, a potassium hydroxide (KOH) test, and microscopic examination of a wet mount of fresh samples of vaginal discharge.” However, the guidelines conclude that “in settings where pH paper, KOH, and microscopy are unavailable, a broad range of clinical laboratory tests … can be used.

For the evaluation of BV, the CDC recommends that “BV can be diagnosed by the use of clinical criteria (i.e., Amsel’s Diagnostic Criteria) (Amsel et al., 1983) or Gram stain”; further, “Other tests, including Affirm VP III (Becton Dickinson, Sparks, MD), a DNA hybridization probe test for high concentrations of *G. vaginalis*, and the OSOM BV Blue test (Sekisui Diagnostics, Framingham, MA), which detects vaginal fluid sialidase activity, have acceptable performance characteristics compared with Gram stain. Although a prolineaminopeptidase card test is available for the detection of elevated pH and trimethylamine, it has low sensitivity and specificity and therefore is not recommended. PCR has been used in research settings for the detection of a variety of organisms associated with BV, but evaluation of its clinical utility is still underway. Detection of specific organisms might be predictive of BV by PCR (Cartwright et al., 2012; Fredricks, Fiedler, Thomas, Oakley, & Marrazzo, 2007). Additional validation is needed before these tests can be recommended to diagnose BV. Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific. Cervical Pap tests have no clinical utility for the diagnosis of BV because of their low sensitivity and specificity (CDC, 2015a).” The guidelines also state that “evidence is insufficient to recommend routine screening for BV in asymptomatic pregnant women at high or low risk for preterm delivery for the prevention of preterm birth (CDC, 2015a)”, which is in compliance with the 2008 USPSTF recommendations (USPSTF, 2008).

The CDC’s most current guidelines regarding BV (CDC, 2021a) state that “BV NAATs should be used among symptomatic women only (e.g., women with vaginal discharge, odor, or itch)

because their accuracy is not well defined for asymptomatic women. 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". The CDC specifically mentions several of the multiplex PCR assays that are available, including the FDA-approved Aptima BV (Hologic) and Max Vaginal Panel (Becton Dickinson).

For the evaluation of vulvovaginal candidiasis, the CDC recommends: "Examination of a wet mount with KOH preparation should be performed for all women with symptoms or signs of VVC, and women with a positive result should be treated. For those with negative wet mounts but existing signs or symptoms, vaginal cultures for *Candida* should be considered (CDC, 2015c)." The most current guidelines for VVC diagnosis state that "vaginal culture or PCR should be obtained from women with complicated VVC to confirm clinical diagnosis and identify non–*albicans Candida*" (CDC, 2021d).

For the evaluation of Trichomoniasis, the CDC recommends: "Diagnostic testing for *T. vaginalis* should be performed in women seeking care for vaginal discharge… The use of highly sensitive and specific tests is recommended for detecting *T. vaginalis.* Among women, NAAT is highly sensitive, often detecting three to five times more *T. vaginalis* infections than wet-mount microscopy, a method with poor sensitivity (51%–65%) (CDC, 2015b; Hollman, Coupey, Fox, & Herold, 2010; Roth et al., 2011)." Regarding point of care testing, it is stated that "Other FDA-cleared tests to detect *T. vaginalis* in vaginal secretions include the OSOM *Trichomonas* Rapid Test (Sekisui Diagnostics, Framingham, MA), an antigen-detection test using immunochromatographic capillary flow dipstick technology that can be performed at the point of care, and the Affirm VP III (Becton Dickinson, Sparks, MD), a DNA hybridization probe test that evaluates for *T. vaginalis*, *G. vaginalis*, and *Candida albicans*. The results of the OSOM *Trichomonas* Rapid Test are available in approximately 10 minutes, with sensitivity 82%–95% and specificity 97%–100% (Campbell, Woods, Lloyd, Elsayed, & Church, 2008; Huppert et al., 2007). Self-testing might become an option, as a study of 209 young women aged 14–22 years found that >99% could correctly perform and interpret her own self-test using the OSOM assay, with a high correlation with clinician interpretation (96% agreement, $\kappa = 0.87$) (Huppert et al., 2010). The results of the Affirm VP III are available within 45 minutes. Sensitivity and specificity are 63% and 99.9%, respectively, compared with culture and TMA; sensitivity might be higher among women who are symptomatic (Andrea & Chapin, 2011; Brown, Fuller, Jasper, Davis, & Wright, 2004; CDC, 2015b)."

In the Sexually Transmitted Infections Treatment Guidelines, 2021, the CDC also mentions the FDA-cleared Aptima *T. vaginalis* assay that may be used for detection of *T. vaginalis* from symptomatic or asymptomatic women (CDC, 2021c).

American Academy of Family Physicians (AAFP)

The AAFP published an article (Hainer & Gibson, 2011) on the diagnosis of vaginitis which states that: "Physicians traditionally diagnose vaginitis using the combination of symptoms, physical examination, pH of vaginal fluid, microscopy, and the whiff test. When combined, these

tests have a sensitivity and specificity of 81 and 70 percent, respectively, for BV; 84 and 85 percent for vulvovaginal candidiasis; and 85 and 100 percent for trichomoniasis when compared with the DNA probe standard…A cost-effectiveness analysis of diagnostic strategies for vaginitis undiagnosed by pelvic examination, wet-mount preparation, and related office tests showed that the least expensive strategy was to perform yeast culture, gonorrhea and chlamydia probes at the initial visit, and Gram stain and *Trichomonas* culture only when the vaginal pH exceeded 4.9. Other strategies cost more and increased duration of symptoms by up to 1.3 days (Hainer & Gibson, 2011)."

In 2018, the AAFP has published the following guidelines:

- "Symptoms alone cannot differentiate between the causes of vaginitis. Office-based or laboratory testing should be used with the history and physical examination findings to make the diagnosis. (C evidence rating)
- Do not obtain culture for the diagnosis of bacterial vaginosis because it represents a polymicrobial infection. (C evidence rating)
- Nucleic acid amplification testing is recommended for the diagnosis of trichomoniasis in symptomatic or high-risk women. (C evidence rating) (Paladine & Desai, 2018)."

U.S. Preventive Services Task Force Recommendations (USPSTF)

In 2020, the USPSTF published recommendations discouraging the use of screening for BV in pregnancy: "The USPSTF recommends against screening for bacterial vaginosis in pregnant persons not at increased risk for preterm delivery". On a similar note, the USPSTF maintains its 2008 recommendation stating "that the current evidence is insufficient to assess the balance of benefits and harms of screening for bacterial vaginosis in pregnant persons at increased risk for preterm delivery" (Owens et al., 2020).

American College of Obstetrics and Gynecology (ACOG)

ACOG published recommendations (ACOG, 2006) for the evaluation of vaginitis in 2006, and reaffirmed in 2017 (ACOG, 2017, 2018), which state: "Evaluation of women with vaginitis should include a focused history about the entire spectrum of vaginal symptoms, including change in discharge, vaginal malodor, itching, irritation, burning, swelling, dyspareunia, and dysuria." Further, "During speculum examination, samples should be obtained for vaginal pH, amine ("whiff") test, and saline (wet mount) and 10% potassium hydroxide (KOH) microscopy. The pH and amine testing can be performed either through direct measurement or by colorimetric testing." With a Level B recommendation, ACOG states, "Microscopy is the first line for diagnosing vulvovaginal candidiasis and trichomoniasis. In selected patients, culture for yeast and *T. vaginalis* should be obtained in addition to standard office-based testing." Additionally, "A vaginal Gram stain for Nugent scoring of the bacterial flora may help to identify patients with BV. Other currently available ancillary tests for diagnosing vaginal infections include rapid tests for enzyme activity from BV-associated organisms, *Trichomonas vaginalis* antigen, and point-of care testing for DNA of *G. vaginalis*, *T. vaginalis*, and *Candida* species; however, the role of

these tests in the proper management of patients with vaginitis is unclear. Depending on risk factors, DNA amplification tests can be obtained for *Neisseria gonorrheae* and *Chlamydia trachomatis* (ACOG, 2006)."

The ACOG published in 2020 Practice Bulletin Number 215 on vaginitis in nonpregnant patients. In these guidelines, the ACOG made these recommendations for diagnostic testing based on good and consistent scientific evidence (Level B):

- "The use of Amsel clinical criteria or Gram stain with Nugent scoring is recommended for the diagnosis of bacterial vaginosis."
- "Nucleic acid amplification testing is recommended for the diagnosis of trichomoniasis."
- "In a symptomatic patient, diagnosis of vulvovaginal candidiasis requires one of the following two findings: 1) visualization of spores, pseudohyphae, or hyphae on wet-mount microscopy or 2) vaginal fungal culture or commercial diagnostic test results positive for *Candida* species."

The ACOG also published recommendations based on limited or inconsistent scientific evidence (Level B), along with a series of recommendations based on consensus and expert opinion (Level C). Those relating to diagnostic testing are reported below:

- "Patients should be retested within 3 months after treatment for *T vaginalis* because of the high rates of infection recurrence." (Level B)
- "Pap tests are not reliable for the diagnosis of vaginitis. Diagnostic confirmation is recommended for incidental findings of vulvovaginal candidiasis, bacterial vaginosis, or trichomoniasis on a Pap test." (Level B)
- "A complete medical history, physical examination of the vulva and vagina, and clinical testing of vaginal discharge (ie. pH testing, a potassium hydroxide [KOH] "whiff test", and microscopy) are recommended for the initial evaluation of patients with vaginitis symptoms." (Level C)

The ACOG mentions in Bulletin Number 215 that an advanced single-swab panel test that combines multiplex PCR and DNA probe technology could be a promising alternative to microscopy for BV, trichomoniasis, and candidiasis ("Vaginitis in Nonpregnant Patients: ACOG Practice Bulletin, Number 215," 2020).

Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines

IDSA has published an updated clinical guideline (Pappas et al., 2016) for the management of candidiasis in which recommendations include diagnosing vulvovaginal candidiasis before proceeding with empiric antifungal therapy. The usual diagnosis is clinical based on signs and symptoms of vaginitis such as pruritus, irritation, vaginal soreness, vulvar edema, erythema and many others. Clinical signs and symptoms are nonspecific and could be attributed to causes other than vulvovaginal candidiasis. Therefore, authors recommend confirming clinical diagnosis by a wet -mount preparation with saline and 10% KOH to demonstrate the presence of yeast and a normal pH. In cases where signs and symptoms are suggestive of vulvovaginal candidiasis, but

microscopic findings and pH are negative, culture testing confirms the diagnosis according to published guidelines. The IDSA also discusses the possible use of PCR in diagnosing invasive candidiasis, even though the guidelines later state that "Cultures of blood or other samples collected under sterile conditions have long been considered diagnostic gold standards for invasive candidiasis…The role of PCR in testing samples other than blood is not established (Pappas et al., 2016)."

In the 2018 IDSA *A guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases*, the IDSA states, "For vaginosis (altered vaginal flora) a Gram stain and recently available microbiome-based assays are more specific than culture and probe testing for *Gardnerella vaginalis* alone… A number of point-of-care tests can be performed from a vaginal discharge specimen while the patient is in the healthcare setting. Although point-of-care tests are popular, the sensitivity and specificity for making a specific diagnosis vary widely and these assays, while rapid, are often diagnostically poor (Miller et al., 2018)." The IDSA notes that the FDA has approved the use of the Max Vaginal Panel by Becton Dickinson in symptomatic females. "Preliminary data show greater specificity of this approach compared to methods that identify only *G. vaginalis*, as well as consistency in both reproducible as well as standardized results (Miller et al., 2018)."

Society of Obstetricians and Gynecologists of Canada (SOGC)

The SOGC published guidelines for the screening and management of BV in pregnancy. These guidelines state that the following:

- "In symptomatic pregnant women, testing for and treatment of bacterial vaginosis is recommended for symptom resolution. Diagnostic criteria are the same for pregnant and non-pregnant women (I-A).
- Asymptomatic women and women without identified risk factors for preterm birth should not undergo routine screening for or treatment of bacterial vaginosis (I-B).
- Women at increased risk for preterm birth may benefit from routine screening for and treatment of bacterial vaginosis (I-B).
- Testing should be repeated one month after treatment to ensure that cure was achieved (III-L) (Yudin & Money, 2017)."

The SOGC also published guidelines regarding the screening and management of trichomoniasis, VVC, and BV. These guidelines state that "Bacterial vaginosis should be diagnosed using either clinical (Amsel's) or laboratory (Gram stain with objective scoring system) criteria (II-2A) (van Schalkwyk & Yudin, 2015)."

VII. State and Federal Regulations, as applicable

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

A search of the term "vaginitis" on the FDA Device database on February 2, 2021, yielded 149 records. Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
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 Proprietary test: Aptima® BV Assay Lab/Manufacturer: Hologic, Inc
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 Proprietary test: BD MAX™ Vaginal Panel Lab/Manufacturer: Becton Dickson and Company
82120	Amines, vaginal fluid, qualitative
83986	pH; body fluid, not otherwise specified
87070	Culture, bacterial; any other source except urine, blood or stool, aerobic, with isolation and presumptive identification of isolates
87149	Culture, typing; identification by nucleic acid (DNA or RNA) probe, direct probe technique, per culture or isolate, each organism probed

87150	Culture, typing; identification by nucleic acid (DNA or RNA) probe, amplified probe technique, per culture or isolate, each organism probed
87210	Smear, primary source with interpretation; wet mount for infectious agents (eg, saline, India ink, KOH preps)
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
87808	Infectious agent antigen detection by immunoassay with direct optical (ie, visual) observation; Trichomonas vaginalis
87905	Infectious agent enzymatic activity other than virus (eg, sialidase activity in vaginal fluid)
Q0111	Wet mounts, including preparations of vaginal, cervical or skin specimens

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

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X. Review/Revision History

Effective Date	Summary
01/01/2023	Literature review did not necessitate modification to coverage criteria.
05/15/2022	Initial Policy Implementation