Diagnosis of Vaginitis

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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.[1] Other causes include vaginal atrophy in postmenopausal women, cervicitis, foreign body, irritants, and allergens.[2]

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.[3-7]

Vulvovaginal candidiasis (VVC) is usually caused by *Candida albicans* but can occasionally be caused by other *Candida* species.[8] It is the second most common cause of vaginitis symptoms (after BV) and accounts for approximately one-third of vaginitis cases.[9,10]

Trichomoniasis is caused by the flagellated protozoan *Trichomonas vaginalis*, which principally infects the squamous epithelium in the urogenital tract: vagina, urethra, and paraurethral glands.[11,12] This policy only addresses testing for *T. vaginalis* in vaginitis panels. For guidance on single organism for *T. vaginalis*, please see AHS-G2157-Diagnostic Testing of Common Sexually Transmitted Infections.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1) For individuals with signs and symptoms of vaginitis, testing of pH, testing for the presence of amines, measurement of sialidase activity, saline wet mount, potassium hydroxide (KOH) wet mount, and microscopic examination of vaginal fluids **MEETS COVERAGE CRITERIA**.

2) For individuals with signs and symptoms of vaginitis, a multi-pathogen panel test using direct probe DNA-based identification of *Gardnerella*, *Trichomonas*, and *Candida* (e.g., BD Affirm™ VPIII) **MEETS COVERAGE CRITERIA**.

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

4) For individuals with complicated vulvovaginal candidiasis (VVC), nucleic acid amplification testing (NAAT) based identification of *Candida* to confirm clinical diagnosis and identify non-albicans *Candida* **MEETS COVERAGE CRITERIA**.

5) For individuals with signs and symptoms of bacterial vaginosis (BV), NAAT specific to the diagnosis of BV (e.g., Aptima® BV; OneSwab® BV Panel PCR with Lactobacillus Profiling by qPCR; SureSwab® Advanced BV, TMA) and single or multitarget PCR testing for the diagnosis of BV **MEETS COVERAGE CRITERIA**.

6) For individuals with signs and symptoms of vaginitis, NAAT panel testing (no more than one test every seven days; see Note 1) designed to detect more than one type of vaginitis (VVC, BV, and/or trichomoniasis; e.g., BD MAX™ Vaginal Panel, NuSwab® VG, Xpert® Xpress MVP) **MEETS COVERAGE CRITERIA**.

7) For asymptomatic individuals, including asymptomatic pregnant individuals at an average or high risk for premature labor, screening for trichomoniasis and bacterial vaginosis **DOES NOT MEET COVERAGE CRITERIA**.

8) For all other situations not described above, nucleic acid testing (NAT) for Candida (i.e., quantitative NAAT testing, direct probe testing, conditions not addressed above) or *Gardnerella* (e.g., direct probe testing) **DOES NOT MEET COVERAGE CRITERIA.**

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 an individual's illness.

9) Testing for microorganisms involved in vaginal flora imbalance and/or infertility using molecular-based panel testing **DOES NOT MEET COVERAGE CRITERIA**.

10) All other tests for vaginitis (e.g., broad molecular panels designed to concurrently test for vaginitis and various other STIs) not addressed above **DO NOT MEET COVERAGE CRITERIA**.

11) Unspecified amplified DNA-probe testing—specifically CPT code 87798—for the diagnostic evaluation of symptomatic women with genitourinary conditions **DOES NOT MEET COVERAGE CRITERIA** for members/enrollees aged 21 years and older.

NOTES:

Note 1: Per CDC recommendations,[13] the longest minimum treatment for an organism included on the allowed vaginitis panels is a seven day course of antibiotics to treat trichomoniasis. NAAT panel testing for all three types of vaginitis should not be repeated before a minimum treatment window has passed. When symptoms persist despite treatment, individual organism testing may be performed within this window.

III. 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
CT	Chlamydia
DNA	Deoxyribose nucleic acid
DOS	Date of service
HIV	Human Immunodeficiency Virus
IDSA	Infectious Diseases Society of America
LDTs	Laboratory developed tests
MDL	Medical Diagnostic Laboratories
NAAT	Nucleic acid amplification testing
NG	Gonorrhoea
NPV	Negative predictive value
OADS	Office of the Associate Director for Science
PCR	Polymerase chain reaction
PMNs	Polymorphonuclear cells
PPV	Positive predictive value
RTPCR	Real-time polymerase chain reaction
SOC	Standard of care
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

IV. 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.[14] 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. 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.[2]

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.[15,16] 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.[15]

Laboratory documentation of the etiology of vaginitis is important before initiating therapy, given the nonspecific nature and considerable overlap of the symptoms.[17-19] Diagnostic testing enables targeted treatment, increases therapeutic compliance, and increases the likelihood of partner notification.[2,9]

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.[2,18]

There are several challenging aspects to the diagnosis of the etiology of vaginitis based on clinical symptoms. Vaginitis is a global term for nonspecific syndrome and must be narrowed down to the distinct causative factors. Traditional methods have included microscopy, pH testing, amine 'whiff' test, and the Amsel criteria, depending on the suspected etiology. However, physicians may find in-office microscopy to be unavailable, time-consuming, and/or inconclusive in achieving a diagnosis – some estimates hold that misdiagnosis of vulvovaginitis approaches 50%.[20] As another confounding factor, coinfections are common in vaginitis, adding difficulty in diagnosis of the three most common organisms if there is mixed vaginitis or coinfection.[2]

Even though studies have shown that PCR methods have a higher specificity and sensitivity than culture and shorter turn-around time in identifying *Candida,*[21-24] their use may be adding to clinical non-specificity. 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."[23] 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.

Overall, microscopy has lower sensitivities and negative predictive values for BV, candidiasis, and trichomoniasis, and yeast when compared to NAAT and culture, respectively.[2] The use of established molecular diagnostic tests as an alternative to traditional methods is an opportunity to improve the diagnosis and management of vaginitis; NAAT tests have already improved detection of trichomoniasis.[2]

Proprietary Tests

DNA hybridization probe tests

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.*[26]

Bacterial Vaginosis tests

AMPLISwab™

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, STIs, and vaginitis (e.g., BV, candidiasis and trichomoniasis). The test requires one swab to test for 23 total organisms, broken down into four categories (seven yeast, 12 bacteria and one reference bacteria, one parasite, and two types of herpes viruses), employing testing methodologies such as automated DNA/RNA extraction, transcription-mediated amplification (TMA), and RT-PCR for the quantification of select organisms implicated in BV.[27]

Aptima® BV

The Aptima® Assay by Hologic is a NAAT that identifies BV. "NAAT detects 3x more mixed infections cases than clinical diagnosis with wet mount and Amsel's criteria."[28] The Aptima BV Assay is a NAAT that utilizes real-time transcription-mediated amplification for the detection and quantification of ribosomal RNA from BV-associated bacteria: *Lactobacillus* (*L. gasseri*, *L. crispatus*, and *L. jensenii*), *Gardnerella vaginalis*, and *Atopobium vaginae*.[29] "The assay reports a qualitative result for BV and does not report results for individual organisms. The assay is intended to aid in the diagnosis of BV on the automated Panther system using clinician-collected and patient-collected vaginal swab specimens from females with a clinical presentation consistent with vaginitis and/or vaginosis."[30]

OneSwab®

OneSwab® by Medical Diagnostic Laboratories (MDL) uses real-time PCR and qPCR to output a graphical representation of the relative concentrations of the microbial flora. The BV (with *Lactobacillus* profiling) qPCR test results are then reported in a text based and graphical format. The graphic format includes a representation of the results of all the quantitative tests included in the panel. The relative ratios of DNA species in the give sample in proportion to one another reflect the relative concentrations of different bacteria in vaginal specimens. According to the website, the panel includes assays to detect *Gardnerella vaginalis* and *Atopobium vaginae,* which are established BV organisms. NAAT is 95% sensitive and 99% specific for these organisms. In addition, two new assays to detect *Megasphaera* species and *Bacterial*

Vaginosis-Associated Bacterium 2 (BVAB2) are included in the BV (with *Lactobacillus* profiling) panel. According to MDL, using NAAT to detect either of these two organisms is up to 99% sensitive and 94% specific for the diagnosis of BV when compared to Amsel Criteria and Nugent Score.[31] Of note, the sensitivity and specificity just described are for the use of NAAT in detecting these microorganisms, as reported by Fredricks, et al. (2007), and are not necessarily the sensitivity and specificity of the MDL *OneSwab®* for BV.

SureSwab® Advanced Bacterial Vaginosis (BV), TMA

The SureSwab® (Quest Diagnostics, Inc.) Advanced Bacterial Vaginosis (BV), TMA uses real-time TMA to screen for microorganisms involved in BV vaginal flora imbalances, including *Lactobacillus* species, *Atopobium vaginae*, and *Gardnerella vaginalis* from a single vaginal swab. It reports a qualitative result for BV and does not report results for individual organisms. The swab can be collected either by a physician or the patient.[33]

OSOM® BVBlue®

The *OSOM® BVBlue®* chromogenic diagnostic point-of-care test is a CLIA-waived test with a reported 10 minute read time. The test detects "elevated vaginal fluid sialidase activity, an enzyme produced by bacterial pathogens associated with bacterial vaginosis including *Gardnerella, Bacteroides, Prevotella,* and *Mobiluncus*." Sekisui Diagnostics reports that the test is "92.8% sensitive, 98% specific versus Gram Stain" with a "1-minute hands-on-time; 10 minute read time," and "instant color change provides clear easy-to-read results."[34]

Combination panel tests for Vaginitis/Vaginosis

Aptima® CV/TV

Aptima® CV/TV assays are NAAT tests that identify "bacterial vaginosis (BV), vulvovaginal candidiasis (Candida vaginitis or CV) and Trichomoniasis (Trichomonas vaginalis or TV) in symptomatic women from one vaginal sample. NAAT detects 3x more mixed infections cases than clinical diagnosis with wet mount and Amsel's criteria." These tests detect and qualitatively report results for the following organisms: *Candida* species group (*C. albicans, C. tropicalis, C. parapsilosis, C. dubliniensis*), *Candida glabrata*, *Trichomonas vaginalis.*[28]

SureSwab®

SureSwab® Advanced Vaginitis, TMA is a test for BV, vulvovaginal candidiasis (*Candidiasis* species), and trichomoniasis (*Trichomonas vaginalis*).[35] In an even more expansive combination test package, Quest offers a "SureSwab® Advanced Vaginitis Plus, TMA" assay which, in addition to detecting organisms associated with BV, trichomoniasis, and vulvovaginal candidiasis, also detects *Chlamydia trachomatis* and *Neisseria gonorrhoeae.*[36]

BD MAX™ Vaginal Panel

The BD MAX™ Vaginal Panel is "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."[37]

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.[2] The microscopic evaluation of BV is usually based on Amsel criteria.[38] 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.[38] If clinical criteria are used to define infection, then reported sensitivity may range from 62 to 100 percent.[39] 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.[17] The Nugent score is also available as a Gram staining scoring system to diagnose BV based on vaginal swab samples.[40] 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 (e.g., rapid antigen and nucleic acid amplification tests) are used for confirming the clinical suspicion of BV. PCR-based assays to quantify BV-associated bacteria[41,42] have good sensitivity and specificity compared with standard clinical tests.[43,44] However, they are expensive and of limited utility.[7]

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;[9] however, nucleic acid amplification tests have become the accepted gold standard for the diagnosis of *T. vaginalis*.[45] 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.[46] Coexistence of *T. vaginalis* and BV pathogens is common, with coinfection rates of 60 to 80 percent.[11,47]

Microscopy is negative in up to 50 percent of patients with culture-confirmed VVC.[48] Since there are no reliable point-of-care tests for *Candida* available in the United States,[49-54] culture must be obtained. PCR methods have high sensitivity and specificity and a shorter turn-around time than culture,[21-24] but they are costly and offer no proven benefit over culture in symptomatic women.[10]

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).[55] 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)."[55] 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, et al. (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%.[56] These results show that this PCR-based assay can diagnose BV in symptomatic women efficiently.

Gaydos, et al. (2017) conducted a 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.[57] 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."[58] It should be noted, however, that these studies only included symptomatic women, and, therefore, the possible clinical non-specificity (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.[59]

Sumeksri, et al. (2005) conducted a study correlated to the *OSOM® BVBlue®* test. The study included 173 pregnant women reported a sensitivity and specificity of 94% and 96% respectively, as compared to Gram stain score. 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).[61] A larger study (n=288 women) reported a sensitivity of 88% and specificity of 91% as compared to the Amsel 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."[62]

Clinical Utility and Validity

Anand, et al. (2020) investigated the accuracy of Papanicolaou smear to diagnose BV 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."[63]

Hilbert, et al. (2016) performed a prospective longitudinal study on the use of molecular assays for the accurate detection and diagnosis of BV using MDL *OneSwab®*. The authors quantified nine organisms associated with vaginal health or disease (*Gardnerella vaginalis, Atopobium vaginae, BV-associated bacteria 2 (BVAB2,* an uncultured member of the order *Clostridiales), Megasphaera phylotype 1 or 2, Lactobacillus iners, Lactobacillus crispatus, Lactobacillus gasseri,* and *Lactobacillus jensenii*) in a total of

149 women were enrolled in the study. DNA was extracted from clinical specimens using mechanical disruption and the QIAamp mini-kit from Qiagen; qPCR assay was used to quantify BV microbes and *Lactobacillus* species. Though the authors evaluated a broad variety of organisms with the potential to be diagnostic markers, results from the study indicated a sensitivity of 92% and specificity of 95% for three that were predictive of diagnosis of BV: *G. vaginalis*, *A. vaginae*, and *Megasphaera phylotypes 1 and 2;* outcomes were 94% PPV, and 94% NPV for BV. The authors summarized their findings by describing the molecular assay as a highly specific laboratory test to identify BV.[64]

The Aptima BV and Aptima CV/TV) NAAT molecular tests detect and qualitatively report results using a proprietary algorithmic analysis. Pathogens addressed by the test include: *Candida* species group (*C. albicans, C. tropicalis, C. parapsilosis, C. dubliniensis*), *Candida glabrata*, *Lactobacillus*, *Gardnerella vaginalis*, *Atopobium vaginae*, and *Trichomonas vaginalis*.[65] Hologic announced the FDA approval of the Aptima BV and Aptima CV/TV vaginitis tests in 2019.[66] Schwebke, et al. (2020) performed a multicenter, prospective clinical study to validate the performance of the Aptima BV and Aptima CV/TV test for bacterial vaginosis, vulvovaginal candidiasis, and trichomonas vaginitis. A total of 1,519 subjects were enrolled in the study. The authors reported sensitivity and specificity for the investigational tests when it came to provider-collected samples at 95.0% and 89.6% for BV. When it came to *Candida* species, sensitivity and specificity was 91.7% and 94.9% respectively; *C. glabrata* sensitivity and specificity was 84.7% and 99.1%; 96.5% and 94.1% for *T. vaginalis.* Patient-collected samples showed similar ranges of sensitivity and specificity. In conclusion, the authors wrote, "In a secondary analysis, clinicians' diagnoses, in-clinic assessments, and investigational-assay results were compared to gold standard reference methods. Overall, the investigational assays had higher sensitivity and specificity than clinicians' diagnoses and in-clinic assessments, indicating that the investigational assays were more predictive of infection than traditional diagnostic methods."[29]

There has been increasing literature and reviews regarding both NAAT and DNA hybridization probe proprietary-based diagnostic performance in the identification of BV. A study by Richter, et al. (2019) compared the performance of three molecular diagnostic assays. The assays included in the study were BD Affirm, Hologic ASR BV Assay, and the Aptima IVD BV Assay. A total of 111 women were enrolled in the study. Women had been given an Affirm test by their provider after describing symptoms that indicated a form of vaginitis. After the collection of additional specimens, samples were run on the different assays. As predicted by clinicians, BV was the most common outcome of diagnosis for 45 of the patients (71%). The sensitivity and specificity for the Hologic ASR assay (diagnosing BV) was 75.6% and 81.8%. The Affirm assay had a sensitivity and specificity of 86.7% and 60.6% for BV, while the Aptima BV IVD assay showed sensitivities and specificities of 84.4% and 86.3%. According to the study, of the three molecular assays that were evaluated, "Aptima BV IVD demonstrated the highest specificity, which may reflect value for the *A. vaginae* target unique to that assay." The study also noted that "although assays that incorporate more bacterial targets are attractive since they reflect the bacterial diversity that has been reported in BV, it is uncertain whether they will provide better diagnostic accuracy to offset the higher cost usually charged for additional targets."[67]

One population health population study initiated by Kong, et al. (2021) noted that molecular testing is both a sensitive and specific approach to testing and also a welcome tool for providers using labor-intensive traditional practices. The authors address the issue of poor compliance by providers with established gold standard guidelines such as the Amsel criteria, as well as a varied and divergent approaches to office diagnostics. The widespread availability of molecular testing could help accomplish the diagnosis of vaginitis in a single visit. The authors conclude that "compared to CE, molecular tests offer high sensitivity and specificity that provide a precise treatment route. In addition to improved

accuracy, recent evidence demonstrates that the combination of sensitive and specific laboratory testing as well as careful patient evaluation have the potential to reduce unnecessary follow-up visits and improve patient care."[68]

Evans, et al. (2024) studied the clinical utilization and costs of syndromic diagnostic testing for vaginitis. The study included data from 1,175,637 patients with ICD-10 codes indicating vaginitis between the years 2020 and 2023, pulled from the IQVIA PharMetrics® Plus database. Patients were divided into two cohorts: patients who did or did not receive a syndromic PCR test within two days. "Patients who received a Syndromic Vaginitis PCR test had significantly fewer outpatient medical services in the 6 months following initial diagnosis compared to those who received no diagnostic test." The authors attributed this result to decreased medical service visits. Patients who received a syndromic PCR saved an average of 2,067 dollars compared to patients who did not receive a syndromic PCR. The authors concluded that "Syndromic Vaginitis PCR testing may be an effective diagnostic tool for reducing costs associated with vaginitis infections."[69]

V. 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 STIs Treatment Guidelines, 2021.[70] 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."[70]

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."[70]

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) or by determining the Nugent score from a vaginal Gram stain."[71] Additional tests are available: "The Osom BV Blue test (Sekisui Diagnostics) detects vaginal sialidase activity. The Affirm VP III (Becton Dickinson) is an oligonucleotide probe test that detects high concentrations of G. vaginalis nucleic acids (>5 x 105 CFU of *G. vaginalis*/mL of vaginal fluid) for diagnosing BV, *Candida* species, and *T. vaginalis*. This test has been reported to be most useful for symptomatic women in conjunction with vaginal pH measurement and presence of amine odor (sensitivity of 97%); specificity is 81% compared with Nugent. . . Finally, the FemExam Test Card (Cooper Surgical) measures vaginal pH, presence of trimethylamine (a metabolic by-product of *G. vaginalis*), and proline aminopeptidase. . . This test has primarily been studied in resource-poor settings, and although it has been reported to be beneficial compared with syndromic management, it is not a preferred diagnostic method for BV diagnosis."[71] The guidelines also state that due to insufficient evidence, "routine screening for BV among asymptomatic pregnant women at high or low risk for preterm delivery for preventing preterm birth is not recommended,"[71] which is in compliance with the 2020 USPSTF recommendations and endorsed by the AAFP.[72]

Regarding NAATs for BV, the CDC states 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. Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific. Cervical Pap tests have no clinical utility for diagnosing BV because of their low sensitivity and specificity."[71]

The CDC provides information on multiple BV NAATs that are available and notes that "these tests are based on detection of specific bacterial nucleic acids and have high sensitivity and specificity for BV (i.e., *G. vaginalis, A. vaginae*, BVAB2, or *Megasphaera* type 1) and certain lactobacilli (i.e., *Lactobacillus crispatus, Lactobacillus jensenii*, and *Lactobacillus gasseri*). They can be performed on either clinician- or self-collected vaginal specimens with results available in <24 hours, depending on the availability of the molecular diagnostic platform. Five quantitative multiplex PCR assays are available: Max Vaginal Panel (Becton Dickinson), Aptima BV (Hologic), *NuSwab®* VG (LabCorp), *OneSwab®* BV Panel PCR with Lactobacillus Profiling by qPCR (Medical Diagnostic Laboratories), and *SureSwab®* BV (Quest Diagnostics). Two of these assays are FDA-cleared (BD Max Vaginal Panel and Aptima BV), and the other three are laboratory-developed tests. The Max Vaginal Panel provides results by an algorithmic analysis of molecular DNA detection of Lactobacillus species (*L. crispatus* and *L. jensenii*) in addition to *G. vaginalis, A. vaginae*, BVAB2, and *Megasphaera* type 1. This test has 90.5% sensitivity and 85.8% specificity for BV diagnosis, compared with Amsel criteria and Nugent score. It also provides results for Candida species and T. vaginalis. The Aptima BV detects *G. vaginalis, A. vaginae*, and certain *Lactobacillus* species including *L. crispatus, L. jensenii, and L. gasseri*, with sensitivity and specificity ranging from 95.0% to 97.3% and 85.8% to 89.6%, respectively (using either clinician- or patient-collected vaginal swabs). The three laboratory-developed tests (*NuSwab® VG, OneSwab®* BV Panel PCR with Lactobacillus Profiling by qPCR, and *SureSwab®* BV) have to be internally validated before use for patient care yet have good sensitivity and specificity, similar to FDA-cleared assays."[71]

The CDC recommended treatment for BV is "Metronidazole 500 mg orally 2 times/day for 7 days OR Metronidazole gel 0.75% one full applicator (5 g) intravaginally, once a day for 5 days OR Clindamycin cream 2% one full applicator (5 g) intravaginally at bedtime for 7 days." For follow-up after treatment, the CDC recommends: "Follow-up visits are unnecessary if symptoms resolve. Because persistent or recurrent BV is common, women should be advised to return for evaluation if symptoms recur."[71]

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."[8] 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.*"[8]

For the treatment of VVC, the CDC states: "Short-course topical formulations (i.e., single dose and regimens of 1–3 days) effectively treat uncomplicated VVC." The CDC lists 13 over-the-counter, prescription, and oral agents which all have treatment courses ranging from one to 14 days. For follow-up testing after treatment, the CDC recommends: "Follow-up typically is not required. However, women with persistent or recurrent symptoms after treatment should be instructed to return for follow-up visits." The CDC also states: "Even women who have previously received a diagnosis of VVC by a clinician are not necessarily more likely to be able to diagnose themselves; therefore, any woman whose

symptoms persist after using an over-the-counter preparation or who has a recurrence of symptoms <2 months after treatment for VVC should be evaluated clinically and tested."[8]

The CDC recommended treatment for trichomoniasis among women is "Metronidazole 500 mg 2 times/day for 7 days." For follow-up testing after treatment, the CDC recommends: "Because of the high rate of reinfection among women treated for trichomoniasis, retesting for T. vaginalis is recommended for all sexually active women approximately 3 months after initial treatment regardless of whether they believe their sex partners were treated. If retesting at 3 months is not possible, clinicians should retest whenever persons next seek medical care <12 months after initial treatment. Data are insufficient to support retesting men after treatment."[13]

American Academy of Family Physicians (AAFP)

The AAFP published an article 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."[73]

In 2018, the AAFP 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)"[14]

The 2018 guidelines state recommendations for follow-up and retesting. For BV recurrence, "Recurrence of bacterial vaginosis is common. Women should be advised to return for treatment if symptoms recur. Routine testing in asymptomatic women and retesting (test of cure) are not recommended because these bacteria can be part of normal flora." For VVC recurrence, "Candidal species and anaerobes can be normal flora in asymptomatic women, so retesting (test of cure) is not recommended in the absence of symptoms." For trichomoniasis recurrence, "Follow-up with retesting as early as two weeks but within three months is recommended because rates of reinfection are high."[14]

In 2025, the AAFP released an updated guideline which highlighted that "studies demonstrate that patients diagnosed with laboratory tests, specifically the nucleic acid amplification test (NAAT), have fewer return visits and lower health care costs than patients diagnosed with clinical evaluation alone, although the wait time for results may lead to care delays. Papanicolaou tests are not reliable for diagnosis of bacterial vaginosis, vulvovaginal candidiasis, or trichomoniasis. If clue cells, hyphae, or Trichomonas is reported on a Papanicolaou test result, confirmatory testing should be performed before initiating treatment." Furthermore, "patients who have been treated for trichomoniasis should be retested with nucleic acid amplification testing 3 weeks to 3 months after treatment."[74]

The AAFP added a section that goes into greater detail on the diagnosis of these specific types and causes:

Bacterial Vaginosis: In the office setting, bacterial vaginosis is often diagnosed using the Amsel criteria with a sensitivity of 77% and specificity of 92% compared with Gram stain, which is the reference standard. Microscopy is convenient for diagnosis but its use may be limited by time, clinician skill, or access to equipment. Multiplex NAAT has shown better sensitivity and specificity for diagnosis of bacterial vaginosis (96.2% or greater and 92.4% or greater, respectively) than clinician diagnosis (83.4% and 85.5%, respectively). However, these newer tests are more expensive than office-based microscopy, which costs $5 to $10 per test. These criteria have not been validated in postmenopausal populations. Rescreening for bacterial vaginosis is unnecessary if symptoms have resolved with treatment. Patients with three or more documented episodes in one year meet the criteria for recurrent bacterial vaginosis.[74]

Vulvovaginal Candidiasis: Diagnosed using microscopy with visualization of yeast hyphae or budding yeast on potassium hydrochloride preparation, vaginal fungal culture, in-office polymerase chain reaction testing, or NAAT. Vaginal fungal culture can provide speciation in recurrent or resistant cases, but results return in several days, which may delay appropriate treatment. Microscopy is a cost-effective test, but its sensitivity (50%–70%) is lower, which can result in missed diagnoses. NAAT, such as the BD Max Vaginal Panel, has better sensitivity (92.8% vs 56.9%) and specificity (94.6% vs 89%) than clinical diagnosis. Patients with recurrent Candida infections should undergo dedicated testing (ie, yeast culture). Yeast culture with susceptibility testing should be considered, especially if the patient remains symptomatic despite adequate treatment.[74]

Trichomoniasis: Diagnosed on saline microscopy by visualization of motile, flagellated protozoa. However, the Centers for Disease Control and Prevention (CDC) recommends NAAT for diagnosis in symptomatic or high-risk populations due to its higher sensitivity than saline microscopy (95%–100% vs 44%–68%). NAAT can be performed using endocervical, vaginal, or urine specimens. DNA probe tests are also available. They have sensitivity and specificity comparable to NAAT but are more expensive.[74]

U.S. Preventive Services Task Force Recommendations

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."[75]

American College of Obstetrics and Gynecology (ACOG)

The ACOG published in 2020 Practice Bulletin Number 215 on vaginitis in nonpregnant patients. These guidelines were reaffirmed in 2022. In these guidelines, the ACOG made these recommendations for diagnostic testing based on good and consistent scientific evidence (Level A):

- "The use of Amsel clinical criteria or Gram stain with Nugent scoring is recommended for the diagnosis of bacterial vaginosis."
- "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 (i.e. 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.[76]

Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines

The IDSA has published an updated clinical guideline 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."[77]

In the 2024 IDSA *Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases*, the IDSA states that like "the initial investigations of NAATs compared to culture for CT [chlamydia] and NG [gonorrhoea], the SOC [standard of care] reference methods for vaginitis limit the validity of interpretation of the new multiplex vaginal panels. Basically, the vaginal Gram stain (Nugent) and Amsel's criteria do not align with each other on either sensitivity or specificity." The IDSA notes "there are 3 FDA-cleared microbiome-based multiplex vaginal NAATs, BD Max™ Vaginal Panel (Becton Dickinson) (for use in women ≥18 years old), Aptima® BV and CV/TV (Hologic) (both approved for use in ≥14 years of age), and the Xpert® Xpress Multiplex vaginal panel (MVP) test (Cepheid) (approved for use in women ≥18 years old)."

"Several commercial labs offer testing for vaginitis, often requiring a specific swab. Providers need to be aware that targets may vary depending on assay platform used. Tests offered vary from FDA-cleared platforms to lab developed (LDTs). FDA-cleared tests have been validated in several publications. All tests are for use in women with symptoms consistent with vaginitis/vaginosis with either a single self-collected or clinician-collected vaginal swab specimen. Importantly, these multiplex tests are not intended for screening asymptomatic patients. They are also not to be used for prognostic purposes or

to be used as a test of cure. In general, multiplex tests have provided more accurate diagnoses for causes of vaginitis, consistently demonstrating higher sensitivity and negative predictive value than clinician diagnosis or POCTs. In addition, a statistically higher overall percent agreement with each of the reference methods than SOC POCTs performed on site demonstrated statistically higher sensitivity for detecting coinfections, most commonly, BV and VVC."

"BV targets and interpretation algorithms differ for each product, but all use multiple vaginal microbiota species for determination of a positive result, making the tests specific for BV. Candida species are identified in groups relative to likelihood of fluconazole susceptibility (fluconazole susceptible, eg, *C. albicans, C. tropicalis, C. parapsilosis, C. dubliniensis* vs fluconazole resistant, eg, *C. glabrata, C. krusei*). In addition, NAATs have been more accurate in identifying mixed and coinfections, both among vaginitis entities (BV, VVC, TV) as well as with CT and NG. Outcome data from both prospective and retrospective review of claims data and studies shows that primary testing with NAATs results in fewer repeat visits, more directed therapy, and less overall cost as the primary testing choice compared to current SOC POC, despite NAAT results compared were not available at the POC. Overall, data suggest that the need for consistent, more accurate diagnosis and directed treatment is needed. A transition to accurate diagnostic testing for vaginitis by multiplex NAATs needs to be thoroughly addressed in future guidelines."[78]

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)."[79]

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)."[80]

Australian STI Management Guidelines for Use in Primary Care

The Australian STI Management Guidelines for Use in Primary Care recommends testing for bacterial vaginitis when symptoms of "abnormal vaginal discharge and/or malodor" are present. The guidelines recommend for specimen collection: "clinician collection ensures visualisation of secretions and measurement of vaginal pH; microscopy can be performed on self-collected or clinician collected swabs smeared on a slide." Overall, "Clinical diagnosis is made using Amsel criteria (see below); if 3 or 4 of the following criteria are present, presumptive treatment can be offered.

1. Thin white/grey homogenous discharge on speculum examination
2. Elevated vaginal pH (pH > 4.5)

3. Whiff test: malodour with addition of potassium hydroxide to vaginal secretions, or if not available, genital malodour on examination
4. Clue cells on microscopy of Gram stain of high vaginal swab."

The guidelines also note that "Isolation of Gardnerella vaginalis (by NAAT) is reported by some laboratories but cannot be used to diagnose bacterial vaginosis as this organism can also be isolated in people with an optimal vaginal microbiota and no bacterial vaginosis. If your laboratory uses NAAT testing, speak to your pathology provider about its comparative performance. Scoring of the vaginal Gram stain (i.e. Nugent score, Ison-Hay method), are increasingly only used in specialised services."[81]

European Confederation of Medical Mycology (ECMM), International Society for Human and Animal Mycology (ISHAM) and the American Society for Microbiology (ASM)

In a joint guideline the ECMM, ISHAM, and the ASM provide updated 2025 recommendations for the diagnosis and management of candidiasis. "Identification of *Candida* to the species level is strongly recommended if treatment is being considered, to guide empirical management, to detect outbreaks, and for surveillance."[82] Recommendations from this joint guideline as they related to testing for *Candida* include the following:

- "Detailed analysis of the patient's history and a thorough physical examination including focused examination of potentially affected organ systems (e.g. the cardiovascular system for endocarditis and the neurological system for meningitis), through the course of all patients with candidaemia is strongly recommended.
- Physical examination is strongly recommended for diagnosis of urinary, mucosal, and more superficial forms of candidiasis and should be guided by signs and symptoms.
- Conventional culture-based diagnostic methods are strongly recommended, despite limited 1005 sensitivity. For adults, 2-3 blood culture sets with each 20 ml blood should be collected when investigating possible candidaemia.
- Currently, no molecular technique is strongly recommended for any patient population or sample type in diagnosing IC, as pathogen detection is restricted to a limited number of species, and its position in routine clinical use is unclear.
- It is strongly recommended to confirm the diagnosis of candidiasis in tissue by culture or by using in situ identification techniques or panfungal PCR followed by sequencing.
- Serum BDG testing for presumed diagnosis of IC and candidaemia is moderately recommended."[82]

VI. Applicable State and Federal Regulations

Food and Drug Administration

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.

On October 28, 2016, the FDA approved an automatic class III designation for the BD MAX™ Vaginal Panel.[37] Following the initial approval, an additional 510(k) Substantial Equivalence Determination Decision Summary was released on October 21, 2019, with the following note: "Routine post market

surveillance activities informed BD of an unanticipated high rate of nonreportable result rate for the BD MAX Vaginal Panel. Through investigations, BD identified four design modifications intended to improve the tolerance of the BD MAX Vaginal Panel without significantly impacting the validated clinical and analytical performance. . . One of the four design modifications was determined to be significant with the potential to affect the safety or effectiveness of the device and is the focus of this submission. The cumulative changes require minor modifications to the labeling."[83]

On May 23, 2019, the FDA approved the use of the Aptima® BV Assay for the detection and identification of bacterial vaginosis. According to the FDA, "the Aptima BV assay is an in vitro nucleic acid amplification test that utilizes real-time transcription-mediated amplification (TMA) for detection and quantitation of ribosomal RNA from bacteria associated with BV, including Lactobacillus (*L. gasseri, L. crispatus*, and L. *jensenii*), *Gardnerella vaginalis*, and *Atopobium vaginae*. The assay reports a qualitative result for BV and does not report results for individual organisms. The assay is intended to aid in the diagnosis of BV on the automated Panther system using clinician-collected and patient-collected vaginal swab specimens from females with a clinical presentation consistent with vaginitis and/or vaginosis."[30]

VII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a guarantee of payment.

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
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
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

CPT	Code Description
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
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
87905	Infectious agent enzymatic activity other than virus (eg, sialidase activity in vaginal fluid)
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 Proprietary test: MYCODART-PCR™ Dual Amplification Real Time PCR Panel for 6 Candida species Lab/Manufacturer: RealTime Laboratories, Inc/MycoDART, Inc
0330U	Infectious agent detection by nucleic acid (DNA or RNA), vaginal pathogen panel, identification of 27 organisms, amplified probe technique, vaginal swab Proprietary test: Bridge Women's Health Infectious Disease Detection Test Lab/Manufacturer: Bridge Diagnostics/ThermoFisher and Hologic Test Kit on Panther Instrument
0505U	Infectious disease (vaginal infection), identification of 32 pathogenic organisms, swab, real-time PCR, reported as positive or negative for each organism Proprietary test: Vaginal Infection Testing Lab/Manufacturer: NxGen MDx LLC
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),

CPT	Code Description
	Herpes simplex viruses 1 and 2, vaginal fluid, reported as detected or not detected for each organism Proprietary test: HealthTrackRx Vaginitis Lab/Manufacturer: HealthTrackRx, Thermo Fisher Scientific
Q0111	Wet mounts, including preparations of vaginal, cervical or skin specimens

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IX. Revision History

Revision Date	Summary of Changes
01/01/2022	Initial Effective Date
07/19/2022	Updated background, guidelines and recommendations, and evidence based scientific references. Literature review did not necessitate modification to coverage criteria. Revisions to CC7 & CC8. Added CC 12. Added code 87801 Revised code disclaimer statement
06/28/2023	Updated background, guidelines and recommendations, and evidence based scientific references. Literature review necessitated the following changes in coverage criteria: CC8, removed "when limited to known pathogenic species" and provided clarifying language. CC8 now reads: "For individuals with symptoms of bacterial vaginosis (BV), NAAT specific to the diagnosis of BV (e.g., Aptima® BV; OneSwab® BV Panel PCR with Lactobacillus Profiling by qPCR; SureSwab® Advanced BV, TMA) and single or multitarget PCR testing for the diagnosis of BV MEETS COVERAGE CRITERIA. Addition of new CC9: "9) NAAT panel testing designed to detect more than one type of vaginitis (VVC, BV, and/or trichomoniasis; e.g., BD MAX™ Vaginal Panel, NuSwab® VG, Xpert® Xpress MVP) DOES NOT MEET COVERAGE CRITERIA. Revisions to CC7 & CC8. Added CC 12. Added codes 0352U, 87801 Updated description for code 81514 to include (Do not report 81514 in conjunction with 87480, 87481, 87482, 87510, 87511, 87512, 87660, 87661). Revised code disclaimer statement Committee approved: 06/28/2023
08/15/2023	Off cycle coding modification: Added PLA code 0330U. Committee approved: 08/15/2023
02/12/2024	Off-cycle Review, no updates outside of the coverage criteria: Following discussion with our clinical advisory board (CAB) and experts in the field, the decision was made to change CC9 from DNMCC to MCC. Now reads: "9) NAAT panel testing designed to detect more than one type of vaginitis (VVC, BV, and/or trichomoniasis; e.g., BD MAX™ Vaginal Panel, NuSwab® VG, Xpert® Xpress MVP) MEETS COVERAGE CRITERIA." Title changed from "Diagnosis of Vaginitis including Multi-target PCR Testing" to "Diagnosis of Vaginitis" Committee approved: 02/12/2024
05/14/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Committee approved: 05/14/2024
05/21/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following updates were made for clarity and consistency:

	Added sialidase activity to CC1, as it is another appropriate diagnostic tool for vaginitis and did not require an independent CC, now reads: "1) For individuals with signs and symptoms of vaginitis, testing of pH, testing for the presence of amines, measurement of sialidase activity, saline wet mount, potassium hydroxide (KOH) wet mount, and microscopic examination of vaginal fluids MEETS COVERAGE CRITERIA." Results in removal of former CC4: "4) For individuals with symptoms of vaginitis, measurement of sialidase activity in vaginal fluid for the diagnosis of bacterial vaginosis MEETS COVERAGE CRITERIA." CC2, CC3, CC4, CC7, and CC8 edited for clarity and consistency. Added CPT code 81515 and 0505U Removed CPT code 0352U Committee approved: 05/21/2025
02/11/2026	CAB Review Q4 2025: Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following updates were made for clarity and consistency: Individual organism testing for T. vaginalis moved to G2157. Results in removal of CC4, CC5, and CC10. Former CC6, now CC4, added "qualitative" to define the correct type of NAAT testing to be used to screen for Candida infection. Now reads: "4) For individuals with complicated vulvovaginal candidiasis (VVC), qualitative polymerase chain reaction (PCR) based identification of Candida to confirm clinical diagnosis and identify non-albicans Candida MEETS COVERAGE CRITERIA." Former CC8, now CC6, added "(no more than one test every seven days; see Note 1)", now reads: "6) For individuals with signs and symptoms of vaginitis, NAAT panel testing (no more than one test every seven days; see Note 1) designed to detect more than one type of vaginitis (VVC, BV, and/or trichomoniasis; e.g., BD MAX™ Vaginal Panel, NuSwab® VG, Xpert® Xpress MVP) MEETS COVERAGE CRITERIA." New CC8: "8) For all other situations not described above, NAAT testing for Candida (e.g., quantitative NAAT testing) DOES NOT MEET COVERAGE CRITERIA." Former CC12, now CC10, edited for clarity. Now reads: "10) All other tests for vaginitis (e.g., broad molecular panels designed to concurrently test for vaginitis and various other STIs) not addressed above DO NOT MEET COVERAGE CRITERIA.) New Note 1: "Note 1: Per CDC recommendations,13 the longest minimum treatment for an organism included on the allowed vaginitis panels is a seven day course of antibiotics to treat trichomoniasis. NAAT panel testing for all three types of vaginitis should not be repeated before a minimum treatment window has passed. When symptoms persist despite treatment, individual organism testing may be performed within this window." Added CPT code 0068U, 0557U Removed CPT code 87661, 87808 Client requested variance: Added new CC11, "Unspecified amplified DNA-probe testing—specifically CPT code 87798—for the diagnostic evaluation of symptomatic women with genitourinary conditions DOES NOT MEET COVERAGE CRITERIA for members/enrollees aged 21 years and older." Committee approved: 02/11/2026

06/17/2026	CAB Review Q2 2026: Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. The following updates were made for clarity and consistency: Direct probe testing to detect vaginitis is only appropriate when part of a multi-pathogen panel. All individual testing for Trichomonas should now be in the STI policy (G2157). Results in the following changes to CC2, CC4, and CC8: CC2: added “a multi-pathogen panel testing using”, as individual direct probe testing provides minimal information and use of direct probe testing should be restricted to the multi-pathogen panel test (e.g., BD Affirm VPIII) and should not be billed individually. CC4: changed qualitative PCR to NAAT, as individual Candida testing should be amplified probe testing, not direct probe testing CC8: changing NAAT to “nucleic acid testing (NAT)”, adding “direct probe testing, conditions not addressed above” to Candida and adding “or Gardnerella (e.g., direct probe testing) Removed CPT code 87660 Committee Approved: 06/17/2026