Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis

**Description of Procedure or Service**

Bacterial Vaginosis (BV) is a condition caused by an imbalance in the normal bacteria vaginal flora. It is a common disorder, especially in individuals of reproductive age. While there is no single known etiologic agent, there is a shift in vaginal flora that involves a depletion of *Lactobacillus* species and overgrowth of other bacteria, including *Gardnerella vaginalis*, *Mycoplasma hominis*, *Peptostreptococcus*, *Mobiluncus* species, and various other anaerobic gram-negative rods. Prevalence of the condition is high, and it is asymptomatic in most cases. According to data from a nationally representative sample of individuals surveyed in 2001 to 2004, the prevalence of BV among individuals ages 14 to 49 in the United States is 29%. BV is often confused with nonbacterial causes of vaginitis, including Candida (i.e., yeast infection, caused by a fungus) and Trichomonas (caused by a parasite).

When symptomatic, BV is associated with characteristic signs and symptoms. The most common sign of BV is an abnormal grayish white vaginal discharge, generally with an unpleasant (often “fishy”) smell. Some individuals experience mild itching. In addition, BV may be a risk factor for conditions such as preterm delivery and spontaneous abortion in pregnant individuals, pelvic inflammatory disease, HIV and other sexually transmitted diseases. However, causality is difficult to demonstrate, especially in this type of situation where these associations may be spurious due to confounding, because both BV and HIV infection are related to multiple sexual partners. Because of potential risks during pregnancy, treatment of BV is indicated for symptomatic pregnant individuals. However, national organizations do not recommend routine screening for BV among pregnant individuals, and national guidelines do not address screening of nonpregnant individuals.

BV resolves spontaneously in a high percentage of individuals. Treatment for symptomatic BV is usually a course of oral antibiotics, either metronidazole or clindamycin. Antibiotic treatment results in a high rate of remission of symptoms, but recurrences are common within the first year after treatment. Probiotics, alone or in conjunction with antibiotics, are also used but their efficacy in improving cure rates or preventing recurrences is not well-characterized.

BV can be diagnosed in the primary care setting based on patient-reported symptoms, clinical findings during vaginal examination and analysis of vaginal discharge. Office-based analysis of vaginal discharge includes a wet mount preparation using saline, an odor (“whiff”) test to detect amines before or after the addition of 10% potassium hydroxide (KOH) and a test of the pH level. Clinical diagnosis generally involves applying the Amsel criteria, which requires 3 of the following 4 to be present in order for a diagnosis of BV to be confirmed:

- vaginal discharge that is homogeneous, thin and whitish gray discharge;
- presence of clue cells on microscopic examination. These are squamous epithelial cells that normally have a sharply defined cell border but in BV, have bacteria adherent to their surfaces and appear to be “peppered” with bacteria;
- pH of vaginal fluid greater than 4.5;
Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis

- a fishy odor of vaginal discharge before or after addition of 10% KOH

In most cases of uncomplicated BV, clinical and microscopic examination of the discharge is sufficient to make a presumptive diagnosis using the Amsel criteria. For patients with a moderate to high probability of BV following clinical and microscopic exam, an empiric treatment trial can be prescribed. Patients who respond to empiric treatment do not require further workup.

A subset of individuals may require more definitive tests to determine whether BV is present. These include individuals with unusual or unexpected signs and symptoms and those in whom it is not possible to exclude other etiologies with certainty. In these cases, laboratory tests are available to assist with making a definitive diagnosis. Gram staining of vaginal discharge samples is the conventional laboratory method of BV diagnosis, and many experts consider is to be the criterion standard for diagnosing BV. Samples are analyzed using criteria such as the Nugent criteria, or a modified version by Ison and Hay.

A limitation of both of the above diagnostic methods (i.e., clinical diagnosis using Amsel criteria and laboratory diagnosis using Nugent, or Ison and Hay criteria) is that they have subjective components and therefore may be imprecise. Gram stain examination, moreover, is time-consuming and requires substantial training, and it is difficult to determine an appropriate clinical response for intermediate scores. The 2 methods of diagnosis can also be used in combination to increase diagnostic accuracy.

Various commercial tests are also available to provide rapid and accurate pH evaluation and amine detection. For example automated devices that measure the volatile gases produced from vaginal samples and a colorimetric pH test are commercially available.

Vaginal culture is not an appropriate diagnostic method to identify BV because it is not caused by the presence of a particular bacterial species.

DNA probes have been developed and are now available to directly detect and quantify the bacteria in vaginal fluid samples. Bacterial DNA is extracted and amplified by PCR methods, using either universal or specific primers. Bacteria are then identified by characterizing their ribosomal DNA (rDNA) sequences. The specific target is typically the ribosomal subunit of the 16SrRNA gene, which is present in all bacteria. The 16SrRNA genes can be amplified by PCR using universal and/or specific primers. The amplified product is then quantified to give an assessment of how many microorganisms are present. In addition to being able to more accurately diagnose health conditions, use of these new techniques has resulted in the identification of previously unrecognized cultivation-resistant organisms in vaginal fluid.

Several commercially available tests measure multiple organisms using PCR technology for the diagnosis of BV. The tests and the organisms in the panels are shown below:

### Components of Commercially Available Multitarget PCR Tests

<table>
<thead>
<tr>
<th>Organism</th>
<th>SureSwab</th>
<th>BD Max</th>
<th>MDL Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopobium vaginae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gardnerella vaginalis</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactobacillus species</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Megasphaera (type 1, type 2, and/or species)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BVAB (type 1 and/or type 2)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

SureSwab (Quest Diagnostics) tests for Lactobacillus species, G. vaginalis, Atopobium vaginae, and Megasphaera species. A. vaginae is a bacterium species which, using molecular-based techniques, has been found to be more common in women with BV than women with normal flora.
Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis

The SureSwab® test involves obtaining vaginal swab specimens and extracting total DNA. Next, real-time PCR is used to quantify the 4 types of bacteria. Results are reported as log cells per mL for each organism (concentrations of all Lactobacilli species are reported together). In addition, the company provides summary interpretive information based on the findings from all tests. Interpretive information accompanying test results classify findings into 1 of the following 3 categories:

Not supportive of BV diagnosis:
- Presence of Lactobacillus species, G. vaginalis levels <6.0 log cells/mL and absence of A. vaginae and Megasphaera species; or
- Absence of Lactobacillus species, G. vaginalis levels <6.0 log cells/mL and absence of A. vaginae and Megasphaera species; or
- Absence of all targeted organisms.

Equivocal:
- Presence of Lactobacillus species, plus G. vaginalis at least 6.0 log cells/mL and/or presence of A. vaginae and/or Megasphaera species.

Supportive of BV diagnosis:
- Presence of Lactobacillus species, G. vaginalis levels at least 6.0 log cells/mL and presence of A. vaginae and/or Megasphaera species.

Quest Diagnostics also offers a SureSwab® bacterial vaginosis/vaginitis test that includes the bacterial vaginosis test, previously described, and tests for Trichomonas vaginalis and 4 Candidiasis species.

Another product, the BD Max, tests for markers of BV and vaginitis. The test uses a similar process to that described for SureSwab. Vaginal swab specimens are collected, DNA is extracted, and real-time PCR is used to quantify targeted organisms. Results of BV marker tests are not reported for individual organisms. Instead, qualitative BV results are reported based on the relative quantity of the various organisms. In addition to the BV markers, the BD Max also tests for the vaginitis markers Candida glabrata, Candida krusei, other Candida species, and Trichomonas vaginalis.

Medical Diagnostics Laboratory offers a Bacterial Vaginosis Panel. Four markers (shown above in Table 1) are assessed using real-time PCR and Lactobacillus is profiled using quantitative PCR.

Regulatory Status

In October 2016, the Food and Drug Administration completed a review of a de novo request for classification of the BD Max™ Vaginal Panel (Becton, Dickinson, Franklin Lakes NJ). The test was granted class II designation, marketing authorization, and is indicated for the direct detection of DNA targets from bacteria associated with bacterial vaginosis (DEN160001).

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). No multitarget quantitative polymerase chain reaction tests for bacterial vaginosis are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. CLIA-approved tests (eg, SureSwab®; Quest Diagnostics, Madison, NJ; Bacterial Vaginosis Panel; Medical Diagnostics Laboratory) are also commercially available.

Related Policies

Identification of Microorganisms Using Nucleic Acid Probes

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.
Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis

Policy

Multitarget polymerase chain reaction (PCR) testing for diagnosis of bacterial vaginosis is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member’s benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis is covered

Not applicable.

When Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis is not covered

Multitarget polymerase chain reaction (PCR) testing for diagnosis of bacterial vaginosis is considered investigational.

Policy Guidelines

Several studies have evaluated the diagnostic accuracy of multitarget PCR tests for BV, including 2 studies evaluating commercially available tests. The studies found sensitivities of 90% to 95% and specificities of 85% to 90% compared with standard methods of diagnosis. As the reference standard, most tests used a combination of the Amsel criteria and Nugent score. The studies generally included symptomatic women, but none focused on women with an indeterminate diagnosis.

Direct evidence of clinical utility is provided by studies comparing health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials. No published studies were identified that evaluated changes in patient management and/or health outcomes when a multitarget PCR test was used to diagnose BV compared with standard methods of diagnosis.

Several diagnostic accuracy studies have found that multitarget PCR tests for BV have relatively high sensitivity and specificity compared with standard testing methods (ie, the Amsel criteria and Nugent score). However, test results are not as high as the other methods, and it is not clear which women might benefit because many can be diagnosed clinically. Data are lacking on use of the tests in women with an indeterminate clinical diagnosis. Additionally, tests use different markers and calculate composite scores differently.

There is insufficient direct and indirect evidence to establish the clinical utility of multitarget PCR tests.

In individuals who have signs or symptoms of bacterial vaginosis (BV) who receive multitarget polymerase chain reaction (PCR) testing, the evidence includes several prospective studies on technical performance and diagnostic accuracy. Relevant outcomes are test accuracy and validity, symptoms, and change in disease status. Several studies have evaluated the diagnostic accuracy of multitarget PCR.
Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis

tests for BV, including 2 studies evaluating commercially available tests. The studies found sensitivities between 90% and 95% and specificities between 85% and 90% compared with standard methods of diagnosis. Most studies used a combination of the Amsel criteria and Nugent scoring as the reference standard. There is a lack of direct evidence on the clinical utility of PCR testing for BV (ie, studies showing that testing leads to better patient management decisions and/or better health outcomes than current approaches). Moreover, a chain of evidence does not currently support multitarget testing because most symptomatic women can be diagnosed with a standard workup and/or a trial of empirical therapy, and it is not clear which subpopulations might benefit most from this test. Studies have not been conducted in the most clinically relevant target population: symptomatic women with indeterminate diagnoses after standard workup. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

There is no one CPT code for this testing. It would be reported with CPT codes for the various infectious agents for which testing was performed. Below is an example of a possible list of codes:

87491
87591
87481
87512
87661
87999: (4 units reported using modifier -59 on 3 of them to report different subspecies testing of Megasphaera was performed. This is incorrect coding as unlisted codes are only reported once since they do not have an assigned value.)

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Policy Implementation/Update Information

7/1/15   New policy issued. Multitarget polymerase chain reaction (PCR) testing for diagnosis of bacterial vaginosis is considered investigational. Policy noticed 7/1/15 for policy effective date 9/1/15. (sk)
Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis

10/30/15  Specialty Matched Consultant Advisory Panel review 9/30/2015. (sk)

1/26/16   Reference added. (sk)

11/22/16  Specialty Matched Consultant Advisory Panel review 9/28/2016. No change to policy statement. (an)


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