Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis

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;
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- 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;
- 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 it 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.

At least 1 commercially available product measures multiple organisms using PCR technology for the diagnosis of BV. This product, SureSwab (Quest Diagnostics) tests for Lactobacillus species, G vaginalis, Atopobium vaginae, and Megasphaera species. A vaginae is a bacterium species named in 1999 and subsequently, using molecular-based techniques, has been found to be more common in individuals with BV than individuals with normal flora.

The SureSwabTotal test involves obtaining vaginal swab specimens and extracting total DNA. Next, realtime PCR is used to quantitate the 4 types of bacteria. Results are reported as log cells per mL for each organism (concentrations of all Lactobacilli species are reported together).
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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 *Lacobacillus* 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.

**Regulatory Status**

No U.S. Food and Drug Administration–cleared multitarget quantitative PCR tests for bacterial vaginosis were identified. The available commercial PCR tests are offered as laboratory-developed tests. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act.

**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.***

**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.
Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis

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

The evidence for multitarget polymerase chain reaction (PCR) testing in patients who have signs or symptoms of bacterial vaginosis (BV) includes several prospective studies on the diagnostic accuracy of PCR assays of individual markers or combinations of markers, and several prospective studies validating the diagnostic accuracy of multitarget tests. Relevant outcomes are test accuracy and validity, symptoms, and change in disease status. None of the studies evaluated a multitarget PCR test that is commercially available in the United States. The available studies suggest that the multitarget PCR tests that were evaluated may have high sensitivity and specificity for diagnosing BV, but it is not possible to determine the true diagnostic accuracy with certainty due to limited research and heterogeneity in methodology (e.g., differences in the included markers, scoring systems, and/or reference tests). However, studies of diagnostic accuracy alone in unselected populations of individuals with BV are inadequate, because most symptomatic individuals can be diagnosed with a standard workup and/or a trial of empirical therapy. Studies have not been conducted in the most clinically relevant target population, symptomatic individuals with indeterminate diagnoses after standard workup. Furthermore, there is a lack of evidence on the clinical utility of PCR testing for BV, i.e., studies showing that testing leads to better patient management decisions and/or better health outcomes than current approaches. 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
Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis


Policy Implementation/Update Information

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<tr>
<th>Date</th>
<th>Event Description</th>
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<td>7/1/15</td>
<td>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)</td>
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<td>10/30/15</td>
<td>Specialty Matched Consultant Advisory Panel review 9/30/2015. (sk)</td>
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<td>1/26/16</td>
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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.