Policy Statement

Multitarget polymerase chain reaction testing for the diagnosis of bacterial vaginosis is considered investigational.

Policy Guidelines

Diagnostic Criteria

Amsel Criteria

The most common diagnostic approach to bacterial vaginosis (BV) is the use of the Amsel criteria. The Amsel criteria require 3 of the following 4 criteria to be present for a diagnosis of BV to be confirmed:

- Vaginal discharge that is homogeneous, thin, and whitish-gray
- Presence of clue cells on microscopic examination, which 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% potassium hydroxide (KOH)

For patients who cannot be diagnosed by the Amsel criteria, other scoring systems are used in conjunction with Gram stain for the laboratory diagnosis of BV: Nugent criteria and Ison and Hay criteria.

Nugent and Ison and Hay Criteria

For the Nugent criteria, levels of 3 types of bacteria - Lactobacillus, Gardnerella/Bacteroides, and Mobiluncus - in vaginal discharge samples are estimated. Levels of Lactobacillus and Gardnerella/Bacteroides are rated on a scale from 0 to 4 based on the number of cells per field magnified at 100 times, and levels of Mobiluncus are rated on a scale from 0 to 2. A composite score is calculated by summing the 3 subscores, as follows:

- Not consistent with BV:
  - Score of 0-3
  - Score of 4-6 with clue cells not present
- Consistent with BV:
  - Score of 4-6 with clue cells present
  - Score of at least 7

Some clinicians include a third, middle category in Nugent scoring, with a total score of 0 to 3 considered normal, 4 to 6 as intermediate/equivocal, and 7 to 10 as definite BV.

The simplified Ison and Hay criteria are as follows:

- Grade 1 (normal): Lactobacillus morphotypes predominate
- Grade 2 (intermediate): Flora are mixed with some Lactobacillus morphotypes and some Gardnerella or Mobiluncus morphotypes are present
- Grade 3 (BV): Gardnerella and/or Mobiluncus morphotypes predominate. Lactobacilli morphotypes are few or absent
Coding
There is no single CPT code for BV 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:

- **87481**: Infectious agent detection by nucleic acid (DNA or RNA); Candida species, amplified probe technique (3 units reported using the modifier -59 on 2 of them to indicate testing for different subspecies of Candida was performed)
- **87491**: Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, amplified probe technique
- **87512**: Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, quantification
- **87591**: Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, amplified probe technique
- **87661**: Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, amplified probe technique
- **87999**: Unlisted microbiology procedure (4 units reported using modifier -59 on 3 of them to report different subspecies testing of Megasphaera was performed. This is incorrect coding because unlisted codes are only reported once since they do not have an assigned value).

Description
Bacterial vaginosis (BV) is a common medical condition resulting from an imbalance in the normal vaginal flora. Although identification of Gardnerella vaginalis has traditionally been associated with BV, there is no single etiologic agent. Most cases are asymptomatic, and most symptomatic cases can be diagnosed using clinical and microscopic evaluation. Multitarget polymerase chain reaction (PCR) testing is proposed as an alternative to currently available laboratory tests to diagnose BV. This test may improve outcomes if it is a more accurate and reliable method to diagnose BV.

Related Policies
- Identification of Microorganisms Using Nucleic Acid Probes

Benefit Application
Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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). 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 must meet the general regulatory standards of the Clinical Laboratory Improvement Act. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Act for high-complexity testing.

**Rationale**

**Background**

**Bacterial Vaginosis**

BV is a condition caused by an imbalance in the normal bacteria vaginal flora. It is common, especially in women of reproductive age. While there is no single known etiologic agent, there is a shift in vaginal flora that involves a depletion of hydrogen peroxide-producing Lactobacillus species with a rise in vaginal pH and overgrowth of other bacteria, including Gardnerella vaginalis, Mycoplasma hominis, Peptostreptococcus, Mobiluncus species, and other anaerobic gram-negative rods.

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

Various commercial tests 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.

Nucleic acid probes of DNA fragments are available to detect and quantify specific bacteria in vaginal fluid samples. Polymerase chain reaction (PCR) methods extract and amplify the DNA fragments using either universal or specific primers. The result can be qualitative (to assess whether a specific microorganism is present) or quantitative (to assess how many microorganisms are present). The technology can be used to measure multiple organisms (e.g., those known to be associated with BV) at the same time and is commercially available as multitarget PCR testing.

(Blue Shield of California Medical Policy: Identification of Microorganisms Using Nucleic Acid Probes addresses the use of nucleic acid probes to detect other microorganisms of clinical significance. This policy includes identification of G. vaginalis which is a single microorganism associated with BV.)

**Proposed Multitarget PCR Test**

Examples of commercially available multitarget PCR tests and the organisms in the panels are shown in Table 1; this may not be an exhaustive list of all commercially available tests.

**Table 1. Components of Commercially Available Multitarget PCR Tests**

<table>
<thead>
<tr>
<th>Organism</th>
<th>SureSwab</th>
<th>BD Max</th>
<th>MDL Panel</th>
<th>NuSwab</th>
<th>GenPath BV Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Atopobium vaginae</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2 Gardnerella vaginalis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3 Lactobacillus species</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>4 Megasphaera (type 1, type 2, and/or species)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>5 BVAB (type 1 and/or type 2)</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

BVAB: bacterial vaginosis-associated bacteria; MDL: Medical Diagnostics Laboratory; PCR: polymerase chain reaction.

The SureSwab Total (Quest Diagnostics) test involves obtaining vaginal swab specimens, extracting total DNA, and quantitating the four types of bacteria using PCR. Results are reported as log cells per milliliter for each organism and concentrations of all Lactobacilli species are reported together then classified into one of the following three categories: not supportive, equivocal, and supportive.
A classification of not supportive of BV diagnosis is based on:
- The presence of Lactobacillus species, G. vaginalis levels <6.0 log cells/mL, and absence of Atopobium vaginae and Megasphaera species; or
- The absence of Lactobacillus species, G. vaginalis levels <6.0 log cells/mL, and absence of A. vaginae and Megasphaera species; or
- The absence of all targeted organisms.

A classification of equivocal is based on:
- The presence of Lactobacillus species, plus G. vaginalis at least 6.0 log cells/mL, and/or presence of A. vaginae and/or Megasphaera species.

A classification of supportive of BV diagnosis is based on the absence of Lactobacillus species, and presence of G. vaginalis levels of at least 6.0 log cells/mL, and presence of A. vaginae and/or Megasphaera species.

Another product, the BD Max (Becton, Dickinson), 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 quantitate targeted organisms. Results of BV marker tests are not reported for individual organisms. Instead, qualitative BV results are reported as positive or negative for BV based on the relative quantity of the various organisms.

Medical Diagnostics Laboratory offers a Bacterial Vaginosis Panel. Markers are shown above in Table 1 and are assessed using real-time PCR and Lactobacillus is profiled using quantitative PCR. GenPath Diagnostics also offers a bacterial vaginosis test.

The NuSwab® Select BV test (Laboratory Corporation of American) uses semiquantitative PCR analysis of three predictive marker organisms of vaginal dysbiosis to generate a total score that is associated with the presence or absence of BV. In this test system, samples with a total score of 0 to 1 are considered negative for BV, samples with a score of 3 to 6 are positive for BV, and samples with a score of 2 are indeterminate for BV.

Several of the manufacturers of the BV tests also have extensions that include other causes of vaginitis such as Trichomonas vaginalis and Candidiasis species.

Literature Review
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Individuals with Signs or Symptoms of Vaginal Vaginosis
Clinical Context and Test Purpose
The purpose of multitarget polymerase chain reaction (PCR) testing in patients who have signs or symptoms of bacterial vaginosis (BV) is as a replacement to current diagnostic strategies so that appropriate treatment is selected and patient outcomes are improved.

This review evaluates whether multimarker PCR testing improves health outcomes compared with standardly used diagnostic tests. These tests have been proposed as a replacement for standard diagnostic tests such as Amsel criteria and Nugent score.
The questions addressed in this evidence review are: In individuals who have signs or symptoms of BV, does multitarget PCR improve net health outcomes?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are patients with signs or symptoms of BV. BV is a condition caused by an imbalance in the normal bacteria vaginal flora. It is common, especially in women 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 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 women surveyed from 2001 to 2004, the prevalence of BV among women ages 14 to 49 years in the United States was 29%.[2] BV may be confused with nonbacterial causes of vaginitis, including candidiasis and trichomoniasis.

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 in association with mild itching or irritation.

BV resolves spontaneously in a high percentage of women, 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.

**Interventions**
The intervention of interest is a multitarget PCR test for BV. Nucleic acid probes of DNA fragments are available to detect and quantify the bacteria in vaginal fluid samples. Bacterial DNA is extracted and amplified by PCR methods, using either universal or specific primers. The result can be qualitative (to assess whether a specific microorganism is present) or quantitative (to assess how many microorganisms are present). The technology can be used to measure multiple organisms (e.g., those known to be associated with BV) at the same time and is commercially available as multitarget PCR testing.

**Comparators**
The comparators of interest are standard diagnostic approaches such as clinical examination and microscopic examination of vaginal specimens.

Gram staining of vaginal discharge samples is the conventional microscopic method of BV diagnosis and requires preparation and analysis of the specimen in the laboratory setting. It remains the historical research criterion standard for diagnosing BV. Gram stained samples are analyzed using the Nugent criteria or a modified version by Ison and Hay.

For the Nugent criteria, levels of three types of bacteria Lactobacillus, Gardnerella/Bacteroides, and Mobiluncus in vaginal discharge samples are estimated. Levels of Lactobacillus and Gardnerella/Bacteroides are rated on a scale from 0 to 4 based on the number of cells per field magnified at 100 times, and levels of Mobiluncus are rated on a scale from 0 to 2. A composite score is calculated by summing the 3 subscores, as listed in Table 2.

### Table 2. Nugent Criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Scoring Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Not consistent with BV</td>
<td>Score of 0-3; or score of 4-6 with clue cells not present</td>
</tr>
<tr>
<td>2  Consistent with BV</td>
<td>Score of 4-6 with clue cells present; or score of at least 7</td>
</tr>
</tbody>
</table>
Some clinicians include a third, middle category in Nugent scoring, with a total score of 0 to 3 considered normal, 4 to 6 as intermediate/equivocal, and 7 to 10 as definite BV.

Table 3 summarizes the simplified Ison and Hay criteria.

### Table 3. Ison and Hay Criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Scoring Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Grade 1 (normal)</td>
<td>Lactobacillus morphotypes predominate</td>
</tr>
<tr>
<td>2 Grade 2 (intermediate)</td>
<td>Flora are mixed with some Lactobacillus morphotypes and some Gardnerella or Mobiluncus morphotypes are present</td>
</tr>
<tr>
<td>3 Grade 3 (bacterial vaginosis)</td>
<td>Gardnerella and/or Mobiluncus morphotypes predominate; lactobacilli morphotypes are few or absent</td>
</tr>
</tbody>
</table>

In practice, the diagnosis of BV can be made based on the presence of at least 3 Amsel criteria (characteristic vaginal discharge, elevated pH, clue cells, fishy odor), which is simple and has a sensitivity of over 90% and specificity of 77% compared with Gram stain.

More specifically, vaginal discharge is characterized as homogeneous, thin, and whitish-gray; clue cells 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; and a “fishy” odor of vaginal discharge before or after addition of potassium hydroxide 10%.

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

### Outcomes

The primary outcomes of interest are test validity, symptom resolution, and cure rate (absence of symptoms and normal vaginal flora).

### Time

The timing for measuring symptom resolution is seven to ten days (i.e., the length of a course of antibiotics). Symptoms could be assessed in the longer term (e.g., a month) to evaluate recurrence of BV.

### Setting

The test would be used in the primary care or specialty care setting (i.e., gynecology).

### Study Selection Criteria

For the evaluation of clinical validity of the tests, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (Amsel, Nugent, or Hay/Ison criteria)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

A publication by Hilbert et al (2016), funded through Medical Diagnostics Laboratory and evaluating markers in that laboratory’s BV Panel, was not selected because it did not include a validation cohort independent of the development cohort.
Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

There are no published studies on the diagnostic accuracy of the SureSwab test or the GenPath test, but information is available on the diagnostic accuracy of the BD Max test, and the NuSwab offered by LabCorp.

Characteristics of the studies are shown in Table 4 and results are shown in Table 5. The studies are briefly described following the tables.

**Table 4. Characteristics of Clinical Validity Studies Assessing BV Tests**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Design</th>
<th>Reference Standard</th>
<th>Threshold for Positive Index Test</th>
<th>Timing of Reference and Index Tests</th>
<th>Blinding of Assessors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 BD Max</td>
<td>Women with symptoms of BV or vaginitis; samples collected in 2015; 53% African American; 25% white; age range, 18-29 y</td>
<td>Prospective, consecutive, multicenter</td>
<td>Nugent score; indeterminate by Nugent diagnosed with Amsel criteria</td>
<td>Automatic reporting based on algorithmic analysis of molecular DNA detection of lactobacilli and bacteria associated with BV</td>
<td>Simultaneous</td>
<td>Yes</td>
</tr>
<tr>
<td>2 FDA decision summary[^8]; Gaydos (2017)[^9]</td>
<td>Women with symptoms of BV or vaginitis; samples collected in 2016-2017; 34% African American, 38% white, age range, 18-49 y</td>
<td>Prospective, multicenter</td>
<td>Nugent score; indeterminate by Nugent diagnosed with Amsel criteria</td>
<td>Score of 3-6 indicates presence of BV</td>
<td>Simultaneous</td>
<td>Yes</td>
</tr>
<tr>
<td>3 NuSwab</td>
<td>Women evaluated at 3 clinics in Alabama in 2011; 87% African American, 13% (50/402) white</td>
<td>Prospective, selection criteria not described</td>
<td>Nugent score; indeterminate by Nugent diagnosed with Amsel criteria</td>
<td>Score of 3-6 indicates presence of BV</td>
<td>Simultaneous</td>
<td>Yes</td>
</tr>
</tbody>
</table>

BV: bacterial vaginosis; RCT: randomized controlled trial.
### Table 5. Results of Clinical Validity Studies Assessing BV Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial N</th>
<th>Final N</th>
<th>Excluded Samples</th>
<th>Prevalence of Condition, %</th>
<th>Clinical Validity (95% Confidence Interval), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 BD Max</td>
<td>1763</td>
<td>1559</td>
<td>1582&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Protocol issues: withdrawn (13), informed consent process incorrect (7), asymptomatic patient enrolled (2), and &gt;1 specimen obtained for same patient (1) TPI: reference standard results not compliant with protocol (130); index test not compliant with protocol (8); index test results not reported (71)</td>
<td>56 90.5 (88.3 to 92.2) &lt;sup&gt;a&lt;/sup&gt; 90.7 (88.6 to 92.5) &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 FDA decision summary&lt;sup&gt;[8]&lt;/sup&gt;; Gaydos (2017)&lt;sup&gt;[9]&lt;/sup&gt;</td>
<td>1763</td>
<td>1559</td>
<td>1582&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>56 90.5 (88.3 to 92.2) &lt;sup&gt;a&lt;/sup&gt; 90.7 (88.6 to 92.5) &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3 NuSwab</td>
<td>1595</td>
<td>1484</td>
<td>Incomplete testing (16); test indeterminate (95)</td>
<td>34 96 (94 to 98)</td>
<td>90 (88 to 92)</td>
</tr>
<tr>
<td>4 Cartwright (2018)&lt;sup&gt;[10]&lt;/sup&gt;</td>
<td>1595</td>
<td>1484</td>
<td>Incomplete testing (16); test indeterminate (95)</td>
<td>34 96 (94 to 98)</td>
<td>90 (88 to 92)</td>
</tr>
</tbody>
</table>

**BV:** bacterial vaginosis; **NPV:** negative predictive value; **NR:** not reported; **PPV:** positive predictive value; **TPI:** test performance issues.

<sup>a</sup> Clinician. <sup>b</sup> Self.

#### BD Max Test

The FDA decision summary and Gaydos et al (2017) for the BD Max test includes a description of a prospective clinical diagnostic accuracy study.<sup>[8][9]</sup> The study included 1763 women with symptoms of BV or vaginitis. Both clinician-collected and self-collected vaginal swabs were obtained, and were analyzed independently. A total of 1559 (88%) clinician-detected and 1582 (90%) self-detected samples were available for analysis.

#### NuSwab

Cartwright et al (2012) published data on a multitarget semiquantitative PCR test including 3 organisms: Atopobium vaginae, Megasphaera type 1, and BVAB2.<sup>[11]</sup> The investigators used separate samples for the development and validation phases and compared the diagnostic accuracy of the multitarget panel with an accepted reference standard. The patient population consisted of 402 women presenting at a clinic for sexually transmitted infections (n=299) or a personal health clinic (n=103). Samples from 169 women were included in the development phase, of which 108 (64%) were positive for BV and 61 (36%) were negative for BV. In the validation phase, the multitarget PCR test was assessed using an additional 227 samples. Results were similar in Cartwright et al (2018), which reported on a multicenter study of 1579 women of whom 538 were positive and 1041 were negative for BV.<sup>[10]</sup> In this publication, the
authors proposed an a-diversity score generated from next-generation sequencing that could be used to resolve discordant PCR and Nugent/Amsel results.

Several studies have reported on the validation of multitarget PCR tests not currently commercially available in the United States.[12][13][14][15] These tests will not be reviewed in full until such time they become available in the United States.

The purpose of gap tables (see Tables 6 and 7) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

Table 6. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Duration of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FDA decision summary; Gaydos (2017)</td>
<td>1</td>
<td>3. No comparison to clinical diagnosis by Amsel alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Cartwright (2012)</td>
<td>3, 4.</td>
<td>3. No comparison to clinical diagnosis by Amsel alone</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 7. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Blinding</th>
<th>Delivery of Test</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FDA decision summary; Gaydos (2017)</td>
<td></td>
<td></td>
<td></td>
<td>2. &gt;10% of samples excluded</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Cartwright (2012)</td>
<td>1. Selection criteria not clear</td>
<td></td>
<td></td>
<td></td>
<td>1. CIs not reported for subgroup in validation cohort</td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

CI: confidence interval.
a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
b Blinding key: 1. Not blinded to results of reference or other comparator tests.
c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
Section Summary: Clinically Valid Diagnostic Accuracy

Several studies have evaluated the diagnostic accuracy of multitarget PCR tests for BV, including three studies evaluating commercially available tests. The studies found sensitivities of 90% to 95% and specificities of 85% to 90%, compared with a reference standard combination of the Amsel criteria and Nugent score. The studies generally included symptomatic women.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

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 health outcomes when a multitarget PCR test was used to diagnose BV compared with standard methods of diagnosis.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Diagnostic accuracy studies have found that multitarget PCR tests for BV have sensitivity ranging from approximately 90% to 95% and specificity ranging from approximately 85% to 90% compared with a reference standard combining Amsel criteria and Nugent score. The studies have not reported the concurrent measurement of diagnostic accuracy of Amsel criteria alone.

The multitarget PCR tests have also not demonstrated improvement in other health outcomes. The tests are not less invasive nor less burdensome for patients because they use the same type of specimen obtained during a pelvic exam that would be needed for microscopy. The multitarget PCRs test also does not provide a diagnosis with faster turn-around than using Amsel criteria. Therefore, a chain of evidence to demonstrate an improvement in the net health outcome compared with Amsel criteria cannot be constructed.

Section Summary: Clinically Useful

A useful test provides information to make a clinical management decision that improves the net health outcome. To improve the net health outcome, the multitarget PCR tests should either improve diagnostic accuracy (sensitivity, specificity) or have similar diagnostic accuracy with improvements in other health outcomes such as patient burden or timeliness of diagnosis.

• If the multitarget PCR tests could demonstrate improved diagnostic accuracy, a chain of evidence could be created because improvements in diagnosis should lead to improvements in appropriate treatment and therefore improvement in health outcomes.
• Nugent is the criterion standard for diagnosis of BV in research studies of BV. The studies of multitarget PCR tests used Nugent criteria as the reference standard with the Amsel criteria used when Nugent were indeterminate.
• Given that the criterion standard is how true and false positives and negatives are defined, multitarget PCR tests cannot show higher sensitivity or specificity than the Nugent criteria.
To demonstrate improvement in diagnostic accuracy over the criterion standard would require direct evidence through reporting of health outcomes such as symptom resolution and recurrences.

In the absence of evidence of improved diagnostic accuracy, to demonstrate improvement in the net health outcome multitarget PCR tests should have similar diagnostic accuracy with improvements in other health outcomes such as patient burden or timeliness of diagnosis.

- In the reported studies, sensitivities ranged from approximately 90% to 95% and specificities ranged from approximately 85% to 90% compared with the Nugent criterion standard.
- Guidelines have recommended that Amsel criteria can be used to diagnose BV in practice. Therefore, to understand the diagnostic accuracy of multitarget PCR tests compared with Amsel criteria, studies should have also concurrently compared Amsel criteria with the Nugent criterion standard. The sensitivity and specificity of Amsel criteria alone compared with Nugent criterion were not reported.
- The multitarget PCR tests are no less invasive nor less burdensome for patients than Amsel criteria for diagnosis because they use the same type of specimen obtained during a pelvic exam that would be needed for microscopy.
- The multitarget PCRs test also does not provide a diagnosis with a faster turn-around than Amsel criteria.
- Multitarget PCR tests might provide benefit in the differential diagnosis of vaginitis. However, the other common causes of vaginitis—vulvovaginal candidiasis and trichomoniasis—can also be diagnosed using the clinical information assessed when applying the Amsel criteria (signs/symptoms, vaginal pH, amine test, microscopy).

In sum, the present studies have not demonstrated improvements in diagnostic accuracy or improvements in health outcomes compared with Amsel criteria alone or compared with the Nugent criterion standard.

Summary of Evidence
In individuals who have signs or symptoms of BV who receive multitarget PCR testing, the evidence includes several prospective studies on technical performance and diagnostic accuracy. The relevant outcomes are test validity, symptoms, and change in disease status. Several studies have evaluated the diagnostic accuracy of multitarget PCR tests for BV, including two 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 (i.e., 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements
Centers for Disease Control and Prevention
The Centers for Disease Control and Prevention (2015) updated its guidelines on sexually transmitted diseases. Regarding the diagnosis of bacterial vaginosis (BV), the guidelines stated:

“BV can be diagnosed by ... clinical criteria (i.e., Amsel’s Diagnostic Criteria) or Gram stain. A Gram stain (considered the gold standard laboratory method for diagnosing BV) is used to determine the relative concentration of lactobacilli ... PCR [polymerase chain reaction] has been used in research settings for the detection of ... organisms associated with BV, but...
Evaluation of its clinical utility is still underway. Detection of specific organisms might be predictive of BV by PCR. Additional validation is needed...."

**American College of Obstetricians and Gynecologists**

Published in 2012 and reaffirmed in 2018, the American College of Obstetricians and Gynecologists has produced a practice bulletin on the prediction of preterm birth. The bulletin stated that BV testing is not recommended as a screening strategy in asymptomatic pregnant women at increased risk of preterm birth.[17]

**U.S. Preventive Services Task Force Recommendations**

The USPSTF (2008) recommendations on screening for BV in pregnancy[18] have stated that:

"The USPSTF recommends against screening for bacterial vaginosis in asymptomatic pregnant women at low risk for preterm delivery." (Grade D recommendation)

"The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for bacterial vaginosis in asymptomatic pregnant women at high risk for preterm delivery." (I statement)

These recommendations are currently in revision.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in October 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

**References**


Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>87481</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Candida species, amplified probe technique</td>
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<tr>
<td></td>
<td>87491</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, amplified probe technique</td>
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</table>
Type | Code | Description
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 | 87512 | Infectious agent detection by nucleic acid (DNA or RNA); Gardnerella vaginalis, quantification
 | 87591 | Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, amplified probe technique
 | 87661 | Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, amplified probe technique
 | 87999 | Unlisted microbiology procedure

**HCPCS**
None

**ICD-10 Procedure**
None

**Policy History**
This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>03/30/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2016</td>
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<td>02/01/2019</td>
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</tbody>
</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.