

Performance of a Vaginal Panel Assay Compared With the Clinical Diagnosis of Vaginitis

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OBJECTIVE: To compare the performance of vaginitis diagnosis based on clinical assessment to molecular detection of organisms associated with bacterial vaginosis, vulvovaginal candidiasis, and *Trichomonas vaginalis* using a vaginal panel assay.

METHODS: This cross-sectional diagnostic accuracy study included 489 enrolled participants from five collection sites where those with vaginitis symptoms had a vaginal assay swab collected during their visit and a clinical diagnosis made. The swab was later sent to a

separate testing site to perform the vaginal panel assay. Outcome measures include positive, negative, and overall percent agreement (and accompanying 95% CIs) of clinical assessment with the vaginal panel assay. $P < .05$ was used to distinguish significant differences in paired proportions between the vaginal panel assay and clinical diagnosis, using the McNemar test. Inter-rater agreement between the two diagnostic approaches was determined using Cohen's kappa coefficient.

RESULTS: Clinical diagnosis had a positive percent agreement with the vaginal panel assay of 57.9% (95% CI 51.5–64.2%), 53.5% (95% CI 44.5–62.4%), and 28.0% (95% CI 12.1–49.4%) for bacterial vaginosis, vulvovaginal candidiasis, and *T vaginalis*, respectively. Negative percent agreement for clinical diagnosis was 80.2% (95% CI 74.3–85.2%), 77.0% (95% CI 72.1–81.4%), and 99.8% (95% CI 98.7–99.9%), respectively. Sixty-five percent (67/103), 44% (26/59), and 56% (10/18) of patients identified as having bacterial vaginosis, vulvovaginal candidiasis, and *T vaginalis* by assay, respectively, were not treated for vaginitis based on a negative clinical diagnosis. Compared with the assay, clinical diagnosis had false-positive rates of 19.8%, 23.0%, and 0.2% for bacterial vaginosis, vulvovaginal candidiasis, and *T vaginalis*, respectively. Significant differences in paired proportions were observed between the vaginal panel assay and clinical diagnosis for detection of bacterial vaginosis and *T vaginalis*.

CONCLUSION: The vaginal panel assay could improve the diagnostic accuracy for vaginitis and facilitate appropriate and timely treatment.

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Between 6 and 10 million health care visits in the United States by women are related to symptoms of vaginitis.^{1,2} The most common causes are bacterial

vaginosis (40–50% of cases), vulvovaginal candidiasis (20–25% of cases), and trichomoniasis (15–20% of cases).³ The laboratory reference gold standards for diagnosis of bacterial vaginosis (Gram staining in combination with Nugent criteria scoring)⁴ and vulvovaginal candidiasis (culture)⁵ are time-consuming, involve a delayed time-to-result, and are not widely available in most clinical settings.⁶ Recent Centers for Disease Control guidelines state that nucleic acid amplification tests have a high sensitivity for detection of *Trichomonas vaginalis*, compared with wet mount microscopy.⁵ Diagnosis of vaginitis typically involves clinical findings, medical history, and in-clinic testing—with the latter representing the most essential component. In-clinic testing for bacterial vaginosis relies on Amsel's criteria (vaginal discharge, clue cells, positive whiff test, and a vaginal pH greater than 4.5).⁷ Wet mount microscopy is used for detection of clue cells; budding yeast or pseudohyphae, indicative of vulvovaginal candidiasis⁵; and visualization of motile trichomonads, indicative of *T vaginalis*.^{5,8}

Traditionally, the diagnosis of vaginitis has been inaccurate.^{9–11} Wet mount microscopy has very low sensitivity for all three causes of vaginitis.¹² Availability of a microscope,^{13,14} appropriate training, and certification (eg, Clinical Laboratory Improvement Amendments)¹⁵ are required to perform microscopy in the clinic setting and to accurately identify the correct causes of vaginitis. Non-microscopy-based diagnostic criteria, with either low sensitivity (eg, vaginal discharge, whiff test) or low specificity (eg, vaginal pH), thus, do not consistently facilitate the appropriate diagnosis and treatment.¹² Women who receive empiric treatment for vaginitis, without a known etiology, are more likely to return for a physician visit within 90 days.¹⁶

New technologies, using molecular (DNA) targets that identify the etiologic factors for vaginitis, have recently been developed to address some limitations associated with onsite testing during clinical visits. Nucleic acid amplification tests can achieve both high sensitivity and specificity for detection of the three main infectious causes of vaginitis. In a cross-sectional diagnostic accuracy study, the BD MAX Vaginal Panel demonstrated higher sensitivity for detection compared with Amsel's criteria for bacterial vaginosis, and compared with wet mount microscopy for vulvovaginal candidiasis and *T vaginalis*, while maintaining a comparable specificity.¹² This work suggests that nucleic acid amplification tests are a diagnostic improvement over the traditional clinical algorithms largely used in settings such as primary care physician offices. The objective of this study was to determine

the agreement of clinical diagnosis (standard of care) with a vaginal panel assay for diagnosis of vaginitis in a real-world setting.

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METHODS

This was a multicenter, prospective, cross-sectional study, which involved five study sites (Appendix 1, available online at <http://links.lww.com/AOG/C480>). All specimens were collected from participants attending visits with a health care professional and were eligible if they reported one or more symptoms of vaginitis (abnormal vaginal discharge; vaginal odor; vaginal itching, burning, or irritation; painful or frequent urination; or painful or uncomfortable intercourse). Enrollment started mid-March 2019 and continued for 10 weeks. The sample size was estimated with the goal of identifying 100 positive participants in the bacterial vaginosis group, 100 positive participants with vulvovaginal candidiasis, and 100 positive participants with *T vaginalis*. Institutional review board approval was obtained by all five participating study sites (Advarra), and an informed consent form was signed before any study-related activities. Each participant was assigned a unique study number for purposes of data deidentification. Demographic information such as the participant's age, ethnicity, medical history, antibiotic use, specimen collection date, and clinical signs and symptoms were determined and recorded at each, respective study site. This report was prepared according to STARD (Standards for Reporting of Diagnostic Accuracy) guidelines for accurate reporting.¹⁷

Clinical diagnosis occurred at the time of the visit without knowledge of the results obtained from the vaginal panel assay, and was based on signs and symptoms related to vaginal discharge and wet mount microscopy-based diagnostic procedures—according to the local standard of care.

Vaginal panel assay testing was performed using a vaginal swab (BD MAX Urine Vaginal Endocervical Specimen Collection Swab) and a sample buffer tube in which the swab was inserted. This vaginal swab can be collected by a health care professional or by the patient (self-collection must occur in a clinical setting). The amplified, molecular-based assay provides qualitative (positive or negative) results for bacterial vaginosis, *Candida* group (consisting of *C albicans*, *C tropicalis*, *C parapsilosis*, and *C dubliniensis* [plus *C glabrata* and *C krusei* separately owing to potential antifungal resistance]), and *T vaginalis*.¹⁸ The assay directly detects DNA associated with vulvovaginal candidiasis and *T vaginalis*, and determines bacterial vaginosis status using a bioinformatics algorithm that detects the presence, absence, and relative load of bacterial vaginosis markers (*Lactobacillus* species [*L crispatus* and *L jensenii*], *Gardnerella vaginalis*, *Atopobium vaginae*, *Megasphaera-1*, and bacterial vaginosis-associated bacteria-2). The vaginal panel assay was performed at a separate testing site in Quebec, Canada. The clinical diagnosis result was not available before conducting the assay.

Outcome measurements included positive, negative, and overall percent agreement for clinical diagnosis compared with the vaginal panel assay. CIs were calculated using the Wilson¹⁹ score method. The McNemar test was used for 2×2 classification to test the difference between paired proportions. The calculated difference is that of marginal proportions ([total proportion of vaginal panel positives] – [total proportion of positives by clinical diagnosis]). The upper- and lower-bound 95% CI values were calculated according to Sheskin.²⁰ $P < .05$ was used to distinguish significant differences (note: $P \geq .05$ indicates only that disagreement between the two diagnostic methods is random). Cohen's kappa is a statistical coefficient that measures the agreement between two raters (reference and test) that each classify items into mutually exclusive categories; $K = (P_o - P_e) / (1 - P_e)$.²¹ Indeterminate and uninterpretable results from the vaginal panel assay were not included for data analyses.

RESULTS

Of the 489 enrolled participants, 487 met the inclusion and exclusion criteria in this study across five

clinic sites. Of the 487 swab specimens collected, 12 were excluded because of specimen noncompliance, and six were excluded because they were tested outside of stability parameters, resulting in 469 evaluable specimens. Of the 469 evaluable specimens, 467 yielded reportable results for bacterial vaginosis, and 466 yielded reportable results for both vulvovaginal candidiasis and *T vaginalis* (Fig. 1). The median age of the enrolled participants was 30 years. The majority of specimens were collected from family planning clinics. The most common symptom type reported was abnormal vaginal discharge (70.8% [345/487]), followed by vaginal itching, burning, or irritation (56.5% [275/487]) (Table 1).

Clinical diagnosis of bacterial vaginosis agreed with vaginal panel assay detection in 144 cases, but 103 cases that were negative by clinical diagnosis were positive by the assay (positive percent agreement 57.9%; 95% CI 51.5–64.2%; Table 2). A total of 178 cases were classified as negative by both diagnostic methods, and 44 cases (false-positive rate 19.8%) were

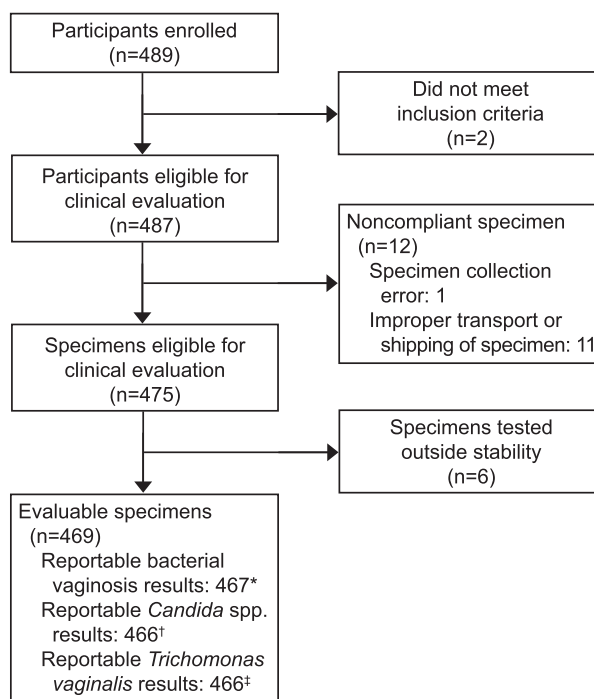


Fig. 1. Reconciliation during enrollment of swab specimens from participants, aged 18 years or older, with symptoms of vaginitis. *One vaginal panel result was indeterminate, and one vaginal panel result was unreportable. †One vaginal panel result was indeterminate, and two vaginal panel results were unreportable. ‡One vaginal panel result was indeterminate, and two vaginal panel results were unreportable.

Broache. Vaginal Panel Assay vs Clinical Diagnosis. *Obstet Gynecol* 2021.

Table 1. Demographic Information and Medical History of the Study Population (N=487)

Characteristic	Value
Age (y)	32.9±11.1 30 (18, 72)
Clinic type	
Family planning	70.2 (342)
Obstetrics and gynecology	20.5 (100)
STD	9.2 (45)
Race-ethnicity	
Asian	0.8 (4)
Black	46.8 (228)
White	46.6 (227)
Other*	5.7 (28)
Hispanic or Latino	29.8 (145)
HIV status	
Seronegative	74.5 (363)
Seropositive	1.2 (6)
Unknown	24.2 (118)
Type of symptom	
Abnormal vaginal discharge	70.8 (345)
Painful or frequent urination	18.9 (92)
Vaginal itching, burning, or irritation	56.5 (275)
Painful or uncomfortable intercourse	12.7 (62)
Vaginal odor	49.5 (241)
Exposure to medications	
Oral antibiotics	11.5 (56)
Vaginal antibiotics	5.3 (26)
Antifungals	4.7 (23)

STD, sexually transmitted disease; HIV, human immunodeficiency virus.

Data are mean±SD, median (minimum, maximum), or % (n).

* Includes Native Hawaiian/Other Pacific Islander, American Indian or Alaskan native, mixed ethnicity, or declined to answer or unknown.

classified as positive by clinical diagnosis but negative by the assay (negative percent agreement 80.2%; 95% CI 74.3–85.2%). The difference between the two diagnostic methods was statistically significant ($P<.001$).

Clinical diagnosis agreed with vaginal panel assay testing for vulvovaginal candidiasis identification in

Table 2. Performance of Clinical Diagnosis Compared With Vaginal Panel for Detection of Bacterial Vaginosis

Clinical Diagnosis	Vaginal Panel Result		Total
	Positive	Negative	
Positive	142	44	186
Negative	103	178	281
Total	245	222	467

Positive percent agreement: 57.9% (95% CI 51.5–64.2%)
 Negative percent agreement: 80.2% (95% CI 74.3–85.2%)
 Overall percent agreement: 68.5% (95% CI 64.1–72.7%)
 Kappa=0.377 (0.296–0.458)

Difference in proportions: 12.2% (95% CI 7.3–17.1%); $P<.001$.

68 cases but called 59 cases negative that were positive by assay testing (positive percent agreement 53.5%; 95% CI 44.5–62.4%; Table 3). Both diagnostic modalities led to negative vulvovaginal candidiasis results in 261 cases, but clinical diagnosis detected 78 positive cases (false-positive rate 23.0%) that were classified as negative by the assay (negative percent agreement 77.0%; 95% CI 72.1–81.4%). The difference between the two diagnostic methods was not significant ($P=.124$).

Clinical diagnosis of *T vaginalis* agreed with vaginal panel assay testing in seven cases but failed to identify 18 cases that were positive by assay testing (positive percent agreement 28.0%; 95% CI 12.1–49.4%; Table 4). A total of 440 cases were classified as negative by both diagnostic methods, one case (false-positive rate 0.2%) was classified as positive by clinical diagnosis but was negative by the assay (negative percent agreement 99.8%; 95% CI 98.7–99.9%). The difference between the two diagnostic methods was statistically significant ($P=.001$).

Of the 103 participants who were vaginal panel assay-positive and clinical diagnosis-negative for bacterial vaginosis, 67 (65.0%) received no treatment (Appendix 2, available online at <http://links.lww.com/AOG/C480>). Of the 59 participants who were assay-positive and clinical diagnosis-negative for vulvovaginal candidiasis, 26 (44.1%) received no treatment (Appendix 3, available online at <http://links.lww.com/AOG/C480>). Finally, of the 18 participants who were assay-positive and clinical diagnosis-negative for *T vaginalis*, 10 (55.6%) received no treatment (Appendix 4, available online at <http://links.lww.com/AOG/C480>).

The data were also stratified by study site (Appendix 1, <http://links.lww.com/AOG/C480>). Three sites provided data from 100 or more participants, and two sites provided data from fewer than 30

Table 3. Performance of Clinical Diagnosis Compared With Vaginal Panel for Detection of Vulvovaginal Candidiasis

Clinical Diagnosis	Vaginal Panel Result		Total
	Positive	Negative	
Yes	68	78	146
No	59	261	320
Total	127	339	466

Positive percent agreement: 53.5% (95% CI 44.5–62.4%)
 Negative percent agreement: 77.0% (95% CI 72.1–81.4%)
 Overall percent agreement: 70.6% (95% CI 66.2–74.7%)
 Kappa=0.292 (0.199–0.385)

Difference in proportions: –4.1% (95% CI –9.0% to 0.8%); $P=.124$.

Table 4. Performance of Clinical Diagnosis Compared With Vaginal Panel for Detection of *Trichomonas vaginalis*

Clinical Diagnosis	Vaginal Panel Result		Total
	Positive	Negative	
Yes	7	1	8
No	18	440	458
Total	25	441	466
Positive percent agreement: 28.0% (95% CI 12.1–49.4%)			
Negative percent agreement: 99.8% (95% CI 98.7–99.9%)			
Overall percent agreement: 95.9% (95% CI 93.7–97.5%)			
Kappa=0.409 (0.198–0.620)			

Difference in proportions: 3.6% (95% CI 1.8–5.5%); $P < .001$.

participants. The average age of the five sites ranged from 28.2 to 43.4 years. There was also some variability in racial and ethnic make-up across the five sites (Appendix 2, <http://links.lww.com/AOG/C480>). There was variability in the overall percent agreement for clinical diagnosis compared with the vaginal panel assay, when the data were stratified by study site (Appendix 5, available online at <http://links.lww.com/AOG/C480>). Overall percent agreement for detection of bacterial vaginosis by clinical diagnosis ranged from 45.0% to 91.7%, depending on the site. Although overall percent agreement for detection of vulvovaginal candidiasis varied in a similar manner, overall percent agreement associated with *T vaginalis* was consistently 90% or greater (Appendix 6, available online at <http://links.lww.com/AOG/C480>).

DISCUSSION

Our findings demonstrate the limited accuracy of clinical diagnosis as an approach for management of vaginitis caused by bacterial vaginosis, vulvovaginal candidiasis, or *T vaginalis* compared with the vaginal assay panel among women with symptoms of vaginitis seen in clinical settings. Consistent with the results here, Schwebke et al¹² previously demonstrated that the vaginal panel assay had better sensitivity (using a laboratory reference standard) than clinical diagnosis for all three causes of vaginitis. We observed that 65%, 44%, and 56% of individuals with vaginal assay-positive, clinical diagnosis-negative results for bacterial vaginosis, vulvovaginal candidiasis, and *T vaginalis*, respectively, went untreated. Conversely, those women who were negative for bacterial vaginosis, vulvovaginal candidiasis, and *T vaginalis*, respectively, by assay testing were still (over) treated according to clinical diagnosis 15%, 17%, and less than 1% of the time (Appendix 7, available online at <http://links.lww.com/AOG/C480>).

Previously, Hillier et al¹⁶ demonstrated that almost half the women with a laboratory-diagnosed cause of vaginitis received at least one treatment that was inappropriate. Not surprisingly, return visits based on persistent vaginitis symptoms were common in that study; occurring in 35%, 17%, and 42% of cases associated with bacterial vaginosis, vulvovaginal candidiasis, and *T vaginalis*, respectively.

We found a significant difference in the paired proportions between clinical diagnosis of bacterial vaginosis and the vaginal panel assay. Although Amsel's criteria represents the primary in-clinic test used to identify bacterial vaginosis,⁵ this modality is subjective,^{22,23} and the accuracy of the different diagnostic components comprising Amsel's criteria differ (Beqaj S, Lebed J, Smith B, Farrell M, Schwebke JR, Rivers CA, et al. Comparison of conventional and modified Amsel's criteria with Nugent score and impact on PCR-based bacterial vaginosis infection status evaluation [abstract]. Int J STD AIDS 2015;26:142.).^{12,18} This suggests that a diagnosis of bacterial vaginosis might vary depending on the type of in-clinic testing involved with the standard of care for any given setting.

Although there was no significant difference in the paired proportions for the vaginal panel assay compared with clinical diagnosis for vulvovaginal candidiasis, clinical diagnosis did result in 26 negative results that were vaginal panel assay-positive but did not receive treatment. Missed diagnoses can lead to recurrent vulvovaginal candidiasis, which can be challenging to treat effectively without an accurate diagnostic tool.^{24,25} Inappropriate treatment for the *C glabrata* species, for example, can lead to the formation of resistance and specific antifungal therapies are recommended to address this cause of vulvovaginal candidiasis.^{26,27}

We observed a significant difference in the paired proportions between clinical diagnosis and the vaginal panel assay for identification of *T vaginalis*. Clinical diagnosis agreed with the vaginal panel assay for positive identification of *T vaginalis* with a sensitivity of only 28%. In a previous study, clinical diagnosis detected trichomoniasis with a sensitivity of approximately 69%.¹² The low prevalence of *T vaginalis* (as identified by the vaginal panel assay, the reference method) here resulted in a low group number of total *T vaginalis*-positive and probably restricted our ability to obtain a completely unbiased assessment of clinical diagnosis, which is reflected in the wide 95% CI (21.0–49.0%). Regardless, the real-world data shown here further highlight the low sensitivity for detection associated with *T vaginalis* vaginitis. Although motile

trichomonads are quite easy to visualize in some instances, the lack of motility that occurs shortly after sample collection, the frequent presence of inflammatory cells that are approximately the same size as trichomonads, and the difficulty with capturing live organisms in the presence of copious discharge all combine to decrease the effectiveness of microscopy as a diagnostic tool for this pathogen.

The reference standards remain as Gram stain with Nugent scoring for bacterial vaginosis and culture for vulvovaginal candidiasis.^{4,5} Nucleic acid amplification testing is generally accepted as a more sensitive diagnostic approach for *T vaginalis* detection than wet mount microscopy.⁵ Challenges with the application of these reference methods exist; Gram stain is a specialized method that not all laboratories offer, and a lengthy turn-around time may occur with culture.⁵ In addition to the accepted reference methods for bacterial vaginosis and vulvovaginal candidiasis, the American College of Obstetricians and Gynecologists also gives a “Level A” rating for the use of Amsel’s criteria for bacterial vaginosis diagnosis and for wet mount microscopy or commercial diagnostic tests for vulvovaginal candidiasis diagnosis.²⁸ Nyirjesy et al found that clinicians often do not follow guidelines set out for the diagnosis of vaginitis owing to lack of access to tools for in-clinic testing and a lack of awareness of guideline recommendations. Findings of this study support the use of U.S. Food and Drug Administration–cleared nucleic acid amplification testing for bacterial vaginosis, vulvovaginal candidiasis, and *T vaginalis*, the three main causes of vaginitis.²⁹ This assay, which can be processed on an instrument placed in either physician office laboratories or reference laboratories, takes approximately 3 hours to run between 2 and 24 samples simultaneously. Therefore, a same-day result is possible if the physician office has the instrument readily available on site. The recommendation for symptomatic patients would be to wait for a result to return before prescribing treatment to reduce incorrect diagnosis and treatment.

There is extensive variability in the accuracy of clinical diagnosis, compared with the vaginal panel assay, when data are analyzed by study site. This could have occurred as a result of demographic makeup, standard operating procedure, variation from site to site, differences in age of the populations, and the inclusion of some sites with low sample size, among other reasons. Regardless of site-to-site availability, sensitive and specific molecular tests should improve the accuracy of diagnosis of vaginitis and will facilitate appropriate treatment.³⁰ Therefore, the American College of Obstetricians and Gynecolo-

gists, the Centers for Disease Control and Prevention, and others who develop treatment guidelines should strongly consider inclusion of molecular-based testing for the diagnosis of all three major causes of vaginitis. In addition, future work could be performed to determine whether the utilization of this vaginal panel assay reduces the overall rate of return visits for vaginitis, compared with clinical diagnosis, especially in women who received no clinical diagnosis and received no treatment, but were subsequently found to have a positive vaginal panel assay result.

It is difficult to know with certainty how a clinical diagnosis of vaginitis, here, relates to a vaginitis diagnosis obtained in routine care settings. Patient specimen collection, testing procedures, or other aspects of patient care are often altered in research studies compared with routine clinical care. Clinical assessment was performed with assistance of a speculum in this study, which is rapidly becoming the exception rather than the rule. Recent recommendations for managing symptomatic women attending emergency departments suggest limited utility of using a speculum.³¹ Additional real-world or health economics outcomes research studies should be employed to further explore this topic.

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