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MINIREVIEW

Diagnostic Tests for Detecting *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in Rectal and Pharyngeal Specimens

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ABSTRACT *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are two of the most often reported bacterial infections in the United States. The rectum and oropharynx are important anatomic sites of infection and can contribute to ongoing transmission. Nucleic acid amplification tests (NAATs) are the mainstays for the detection of *C. trachomatis* and *N. gonorrhoeae* infections owing to their high sensitivity and specificity. Several NAATs have been evaluated for testing in rectal and pharyngeal infections. A few assays recently received clearance by the Food and Drug Administration, including one point-of-care test. Those assays can be used for testing in symptomatic individuals, as well as for asymptomatic screening in certain patient populations. Routine screening for *C. trachomatis* in pharyngeal specimens is not recommended by the Centers for Disease Control and Prevention, though it is often performed due to the use of multiplex assays. While expanding the types of settings for screening and using self-collected rectal and pharyngeal specimens can help to increase access and uptake of testing, additional research is needed to determine the potential benefits and costs associated with increased screening for rectal and pharyngeal *C. trachomatis* and *N. gonorrhoeae* infections on a population level.

KEYWORDS *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, diagnostics, nucleic acid technology, oropharyngeal infection, rectal infection

Chlamydia trachomatis and *Neisseria gonorrhoeae* are the two most common bacterial sexually transmitted infections. In the United States, approximately 4.0 million *C. trachomatis* infections occur every year, and there are 1.6 million *N. gonorrhoeae* infections (1, 2). Together, they account for more than 200 million infections each year worldwide (3). Marginalized populations who have been historically disadvantaged, such as racial and ethnic minorities, as well as sexual minorities, including some gay, bisexual, transgender, and other men who have sex with men (MSM), are disproportionately affected by *C. trachomatis* and *N. gonorrhoeae* infections (2).

Rectal and pharyngeal infections play an important role in the epidemiology of *C. trachomatis* and *N. gonorrhoeae*, especially in MSM. Rectal *chlamydia* and gonorrhea have been associated with increased risk for HIV transmission and acquisition (4, 5). Pharyngeal *C. trachomatis* and *N. gonorrhoeae* infections can also be an important contributor to genital infections (6, 7). Moreover, pharyngeal infections are considered to be a reservoir for antimicrobial resistance (AMR) in *N. gonorrhoeae*, which is becoming of increasing concern worldwide (8, 9). Rectal and pharyngeal infections tend to be asymptomatic; thus, infections at these anatomical sites are typically detected through screening. Among MSM, it is estimated that up to 70% of *C. trachomatis* and *N. gonorrhoeae* infections could be missed if only urogenital testing is performed (10–12).

This minireview will focus on the current state of diagnostic tests for the detection of rectal and pharyngeal *C. trachomatis* and *N. gonorrhoeae* infections, as well as provide

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updates on ongoing areas of research regarding diagnostic testing at these anatomic sites.

DETECTION OF RECTAL AND PHARYNGEAL *C. TRACHOMATIS* AND *N. GONORRHOEAE* INFECTIONS

Due to their high sensitivity and specificity, nucleic acid amplification tests (NAATs) are recommended for the detection of urogenital *C. trachomatis* and *N. gonorrhoeae* infections (13). Until recently, no NAATs had received Food and Drug Administration (FDA) clearance for detecting rectal and pharyngeal *C. trachomatis* and *N. gonorrhoeae* infections. However, a recent clinical trial evaluated the performance of three diagnostic assays to detect *C. trachomatis* and *N. gonorrhoeae* in pharyngeal and rectal specimens (14). The assays evaluated were the Xpert CT/NG assay (Cepheid, Sunnyvale, California), the Aptima Combo 2 assay (Hologic, Inc., San Diego, CA), and the Abbott RealTime CT/GC assay (Abbott Laboratories, Abbott Park, Illinois). The evaluation was a cross-sectional study including a total of 2,598 patients seeking sexually transmitted infection (STI) testing at 9 clinics in 7 U.S. states. Performance of each assay was compared to a composite reference standard consisting of the other two assays, as well as a tie-breaker, if needed. Most study participants were male (79%) and were asymptomatic (88%). The prevalence of *C. trachomatis* was 2.0% in the pharynx and 8.7% in the rectum; the prevalence of *N. gonorrhoeae* was 8.1% in the pharynx and 7.9% in the rectum. Overall, the positive percent agreement (PPA) was high for all assays, although it was noted that the PPA was consistently lower for the Abbott RealTime CT/NG assay. Overall, the PPA was lower for rectal *C. trachomatis* infections across all three assays. The negative percent agreement was high for rectal and pharyngeal specimens across all three assays.

The results of that study were used to support regulatory clearance by the FDA for two of the assays. In May 2019, the FDA cleared the Aptima Combo 2 and the Xpert CT/NG assays for the detection of *C. trachomatis* and *N. gonorrhoeae* in rectal and pharyngeal specimens. Regulatory approval for the remaining assay in that evaluation, the Abbott RealTime CT/NG assay, was not sought. In January 2021, the FDA cleared the cobas CT/NG assay (Roche Molecular Systems, Inc., Branchburg, NJ) for detection of *C. trachomatis* and *N. gonorrhoeae* in rectal and pharyngeal specimens based on findings from another evaluation study (15).

TEST CHARACTERISTICS AND ANALYTICAL EVALUATION

In addition, several assays have reported analytical evaluations for the detection of *C. trachomatis* and *N. gonorrhoeae* in rectal and pharyngeal specimens. Those results will be discussed in detail here.

Hologic Aptima Combo 2. The Aptima Combo 2 assay (Hologic, Inc., San Diego, CA) is a target amplification nucleic acid probe test that uses target capture and transcription-mediated amplification (TMA) to qualitatively detect rRNA from specific regions in *C. trachomatis* (23S rRNA) and *N. gonorrhoeae* (16S rRNA) on the Panther system (16). The assay is FDA-cleared for use in male and female urine specimens, clinician-collected endocervical, vaginal, throat, and rectal specimens and male urethral swab specimens, as well as self-collected vaginal specimens; all specimen types can be used in asymptomatic and symptomatic individuals.

In the analytical specificity evaluation for rectal and pharyngeal specimens, the assay was tested against 44 microorganisms found in pharyngeal and rectal specimens; only the *C. trachomatis*- and *N. gonorrhoeae*-positive specimens were detected (100% analytical specificity). The assay's limits of detection (LoD), as well as the sensitivity and specificity from clinical studies, for *C. trachomatis* and *N. gonorrhoeae* in rectal and pharyngeal specimens are shown in Table 1.

Roche cobas CT/NG assay. The cobas CT/NG assay (Roche Molecular Systems, Inc., Branchburg, NJ) is a qualitative real-time PCR test that detects two DNA targets in *C. trachomatis*, within the cryptic plasmid and the *ompA* gene, and two conserved DNA

TABLE 1 Assays available for the detection of *C. trachomatis* and *N. gonorrhoeae* in rectal and pharyngeal specimens[a]

Assay name	Manufacturer	Platform	Infection type	Target(s)	LoD	Analytical specificity (%)	Clinical sensitivity (%)		Clinical specificity (%)		Reference(s)
							Rectal	Pharyngeal	Rectal	Pharyngeal	
Aptima Combo 2	Hologic, Inc.	Panther	CT	23S rRNA	0.007 IFU/mL	100	91.6	88.2	98.9	99.7	14, 16
			NG	16S rRNA	0.10 CFU/mL	100	97.5	96.1	99.5	98.9	
Cobas CT/NG	Roche Molecular Systems, Inc.	6800/8800	CT	DNA (cryptic plasmid + *ompA*)	2–40 EB/mL	100	95.1	100	99.2	99.8	15
			NG	DNA (2 sequences in DR-9 region)	0.08–0.2 CFU/mL	100	99.0	100	99.3	98.9	
RealTime CT/NG[b]	Abbott Molecular, Inc.	m2000	CT	DNA (plasmid)	Rectal: 12.8 EB/mL Pharyngeal: 2.56 EB/mL	100	83.0	84.0	99.1	99.8	14, 18
			NG	DNA	0.0256 CFU/mL	100	88.3	84.8	99.6	99.5	
Alinity m STI[c]	Abbott Molecular, Inc.	Alinity m	CT	rRNA	0.5 IFU/ assay	100	94.5	93.3	99.6	99.9	19
			NG	DNA (*ompA*)	1.5 CFU/ assay	100	97.2	95.2	99.5	99.3	
Xpert CT/NG	Cepheid	GeneXpert	CT	DNA	Rectal: 88–161 EB/mL Pharyngeal: 161–225 EB/mL	100	86.0	95.9	99.4	99.7	14, 20
			NG	DNA (two targets)	Rectal: 6.4–7.1 CFU/mL Pharyngeal: 1.2–2.7 CFU/mL	100	91.2%	94.7	99.6%	98.8	

[a]CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; LoD, limit of detection; IFU, inclusion-forming units; EB, elementary bodies.
[b]Not FDA cleared.
[c]Assay is CE-marked but not FDA-cleared for use in rectal and pharyngeal specimens.

sequences in *N. gonorrhoeae*, within the DR-9 region. The assay can be used on the cobas 6800 and 8800 platforms. The assay is FDA-cleared for use in male and female urine, self-collected vaginal swabs, and clinician-collected vaginal, endocervical, oropharyngeal, and rectal swab specimens; all specimen types can be used in asymptomatic and symptomatic individuals.

In the analytical evaluation for pharyngeal and rectal specimens, the analytical specificity was determined using 178 microorganisms, and none produced a positive result (100% analytical specificity) (15). In the clinical evaluation for rectal and pharyngeal specimens, the sensitivity and specificity of *C. trachomatis* and *N. gonorrhoeae* infections at those anatomic sites were determined using a composite reference standard, which was composed of two other commercial assays. The sensitivity and specificity values for each infection and anatomic site are shown in Table 1.

Abbott RealTime CT/NG assay. The Abbott RealTime CT/NG assay (Abbott Laboratories, Abbott Park, Illinois) is an *in vitro* PCR assay for the direct, qualitative detection of the plasmid DNA of *C. trachomatis* and the genomic DNA of *N. gonorrhoeae* that is run on the Abbott m2000 RealTime system. Currently, the assay is approved by the FDA only for urogenital specimens. However, the clinical performance of the assay was evaluated in the aforementioned clinical study to help determine the anatomic site infected standard. The Abbott RealTime CT/NG assay was associated with lower sensitivities for *C. trachomatis* and *N. gonorrhoeae* at rectal and pharyngeal sites compared to the other assays (14). Sensitivity and specificity values from the clinical study are shown in Table 1.

An analytical evaluation of the Abbott RealTime CT/NG assay was performed as part of that study and was reported separately (18). The analytical specificity using 28 microorganisms produced negative test results (100% analytical specificity) (18).

Abbott Alinity m STI assay. The Alinity m STI assay (Abbott Molecular, Inc., Des Plaines, IL) is an *in vitro* RT-PCR assay performed on the automated Alinity m system for the qualitative detection and differentiation of *C. trachomatis* and *N. gonorrhoeae*, as well as *Trichomonas vaginalis* and *Mycoplasma genitalium*. The assay targets rRNA sequences in *C. trachomatis* and DNA sequences within the *ompA* gene in *N. gonorrhoeae*. While the assay has not received FDA clearance for rectal or pharyngeal specimens, it has received a CE-mark for *C. trachomatis* and *N. gonorrhoeae* detection using rectal and pharyngeal specimens. The sensitivity and specificity values for *C. trachomatis* and *N. gonorrhoeae* in rectal and pharyngeal specimens are shown in Table 1. The analytical evaluation determined the analytical specificity to be 100% for rectal and pharyngeal specimens, using 180 microorganisms (19).

Cepheid Xpert CT/NG assay. The Xpert CT/NG assay is performed on the GeneXpert instrument (Cepheid, Sunnyvale, CA). It is a qualitative, *in vitro*, real-time PCR test for the automated detection and differentiation of DNA from *C. trachomatis* and *N. gonorrhoeae*. The GeneXpert instrument is modular, can fit on a table-top, and provides test results within 90 min, making it an option for point-of-care testing with same-day test results for patients. The assay uses one chromosomal target in *C. trachomatis* (CT1) and two noncontiguous chromosomal targets for *N. gonorrhoeae*, both of which must be positive to return a positive result (20). The assay is FDA-cleared for use in urine, patient-collected vaginal swabs, and clinician-collected endocervical, pharyngeal, and rectal swabs from asymptomatic and symptomatic individuals. The clinical performance of the assay in rectal and pharyngeal specimens was evaluated in the previously mentioned study. The sensitivity and specificity values for rectal and pharyngeal specimens are shown in Table 1, along with the LoD and the analytical specificity using 84 microorganisms.

SCREENING RECOMMENDATIONS BY POPULATION

The CDC published recommendations for *C. trachomatis* and *N. gonorrhoeae* screening in the updated 2021 CDC STI Treatment Guidelines (21). The recommendations for *C. trachomatis* and *N. gonorrhoeae* are summarized in Table 2.

For cisgender women, screening for rectal *C. trachomatis* and *N. gonorrhoeae* is recommended based on sexual behavior and potential exposures, as well as through

TABLE 2 Screening recommendations for *C. trachomatis* and *N. gonorrhoeae* by population group and anatomic site according to the CDC[a]

Population group for Screening	Subpopulation for Screening	Infection type	Anatomic sites	Frequency
Women	All sexually active women <25 yrs of age and sexually active women >25 yrs of age at increased risk	CT	Urogenital	Annual
			Rectal; considered based on exposure and shared decision making	Retest 3 mo following treatment
			Pharyngeal; none	
		NG	Urogenital	
			Rectal; considered based on exposure and shared decision making	
			Pharyngeal; considered based on exposure and shared decision making	
Heterosexual men	High-prevalence settings (e.g., STI clinic, correctional facilities, adolescent clinics, etc.)	CT	Urogenital; screening can be considered based on risk assessment	Frequency not defined
			Rectal; none	
		NG	Screening is not recommended	
Men who have sex with men		CT	Urogenital	Annual
			Rectal	Screening every 3 mo is indicated for those at increased risk and those taking HIV PrEP
			Pharyngeal; none	
		NG	Urogenital	
			Rectal	
			Pharyngeal	
Transgender and gender-diverse persons	Screening recommendations based on anatomy	CT	Urogenital (cervical/vagina/vaginoplasty)	Annual for those <25 yrs of age with a cervix or those >25 yrs, with a cervix, and at increased risk
			Rectal; considered based on exposure and shared decision making	
			Pharyngeal; none	Undefined for rectal/pharyngeal screening
		NG	Urogenital (cervical/vagina/vaginoplasty)	
			Rectal; considered based on exposure and shared decision making	
			Pharyngeal; considered based on exposure and shared decision making	

[a]CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; STI, sexually transmitted infection; PrEP, preexposure prophylaxis.

shared clinical decision making, whereby the decision to screen is guided by a process in which clinicians and patients work together to choose which tests are most appropriate. Screening for pharyngeal *C. trachomatis* is not recommended for cisgender women, but screening for pharyngeal *N. gonorrhoeae* is recommended based on shared clinical decision making.

Among heterosexual men in low-prevalence settings, the CDC guidelines do not recommend routine screening for rectal and pharyngeal infections. However, screening can be considered in higher-prevalence settings, such as adolescent clinics, STI clinics, or correctional facilities.

For MSM, the CDC guidelines recommend screening for rectal *C. trachomatis* and *N. gonorrhoeae* at least annually and every 3 months for those at increased risk for infections and those taking HIV preexposure prophylaxis (PrEP). Among MSM, screening for pharyngeal *N. gonorrhoeae* annually, and every 3 months for those at increased risk for infections and those taking HIV PrEP, is currently recommended.

For transgender and gender-diverse persons, the screening recommendations for *C. trachomatis* and *N. gonorrhoeae* are based upon the patient's sexual behavior and anatomy. Screening for rectal *C. trachomatis* and *N. gonorrhoeae* infections and pharyngeal *N. gonorrhoeae* infections can be considered based on shared clinical decision making.

In the United States, the prevalences of *C. trachomatis* and *N. gonorrhoeae* are highest among adolescents ages 15 to 24 years old, making them an important population for screening. While the prevalences of STIs are lower among youth ages <15 years compared to those 15 to 24 years, they are still an important age group, as earlier initiation of sexual activity is associated with higher risk for STIs (21). The CDC recommends routine screening for *C. trachomatis* and *N. gonorrhoeae* for all sexually active adolescents, according to various age, sexual behavior, and anatomic classifications. It is important to note that minors in all 50 states and the District of Columbia are allowed to consent to their own STI testing and services, although the ages for consent

vary according to state (22). There are special considerations for testing in minors, such as confidentiality, partner testing and notification, and legal considerations (21). Further screening recommendations for children <13 years old and legal criteria, including in cases of suspected child sexual abuse, are covered in a recent review (23).

For people living with HIV infection, screening for *C. trachomatis* and *N. gonorrhoeae* infections should be done at the initial HIV clinical visit and at least annually thereafter. Among people living with HIV infection who remain at higher risk for STIs, screening for *C. trachomatis* and *N. gonorrhoeae* infections every 3 months is recommended. Screening at the pharynx or rectum should be based upon sexual behavior.

The CDC guidelines do not recommend screening for pharyngeal *C. trachomatis* infections. However, most laboratories in the United States use multiplex assays, combining both *C. trachomatis* and *N. gonorrhoeae* targets, resulting in testing for *C. trachomatis* in pharyngeal specimens, though it is not recommended and might not be ordered by a clinician. Due to regulations, laboratories are not allowed to report test results unless the test was ordered by a clinician, which creates an issue for the laboratories, as they need to blind unordered test results from multiplex assays. Manufacturers could aid in this problem by allowing single-test options for *C. trachomatis* and *N. gonorrhoeae* or by providing software that masks unordered test results. Another option is for clinical microbiology laboratories to perform verification for single-test assays in rectal and pharyngeal specimens.

POINT-OF-CARE TESTS

The timely diagnosis and effective treatment of *C. trachomatis* and *N. gonorrhoeae* infections are important for public health, as they might halt further transmission and avoid severe sequelae caused by these infections. Point-of-care tests can aid in the timely diagnosis and treatment of *C. trachomatis* and *N. gonorrhoeae* infections by reducing time to treatment and loss to follow-up, improving antibiotic stewardship, and offering the flexibility of being performed by nonlaboratory staff (24, 25). In addition, an inexpensive point-of-care test that does not require an extensive laboratory staff or infrastructure will have a critical role in low-resource settings, where there is an urgent need to address health equity issues related to access to diagnostic tests (17, 26).

Recently, several new point-of-care tests have been developed and approved for diagnosing urogenital *C. trachomatis* and *N. gonorrhoeae*. The binx io CT/NG assay (binx Health, Inc., Boston, MA) is run on the binx io desktop system. It has been FDA-cleared for use in self- or clinician-collected female vaginal swabs and male urine specimens. The 30-min test performed well in a cross-sectional clinical evaluation study (27). In March 2021, the platform received a clinical laboratory improvements amendment (CLIA) waiver. Another promising rapid point-of-care test is the Visby Medical sexual health test (Visby Medical, San Jose, CA), which is a single-use device that detects *C. trachomatis* and *N. gonorrhoeae*, in addition to *Trichomonas vaginalis*. In August 2021, the device received FDA clearance and a CLIA-waiver for use in self-collected female vaginal specimens (28). The clinical performance of the assay was recently evaluated in a cross-sectional study (29). Those tests are promising, yet data regarding their use with rectal and pharyngeal specimens are not yet available.

Currently, the Xpert CT/NG assay, run on the GeneXpert instrument, is the only point-of-care test that is FDA-cleared for use in rectal and pharyngeal specimens. The assay returns results within 90 min and has been used in a variety of clinical settings to provide same-day test results and treatment. The Dean Street Clinic in London, United Kingdom, has used that system on self-collected specimens to provide same-day test results. Use of the system was associated with a substantial decrease in time to treatment (30). The Xpert CT/NG assay was evaluated in self-collected rectal and pharyngeal specimens in a study among adolescents at high risk for STIs in Los Angeles, CA, and New Orleans, LA. Investigators found self-collection to be accurate, and there was also a marked reduction in the time to treatment (31, 32). The Xpert CT/NG assay has also been evaluated for use in low-resource settings, where it can improve diagnosis and

same-day treatment in populations with lower access to laboratory-based NAATs (33, 34). While the Xpert CT/NG assay can provide test results at the point of care, it is not currently a CLIA-waived test. It must be performed in laboratories capable of performing moderate- or high-complexity testing.

FUTURE DIRECTIONS

Self-collection of rectal and pharyngeal specimens for *C. trachomatis* and *N. gonorrhoeae* testing using NAATs performs well compared to clinician-collected specimens and offers advantages related to increased patient satisfaction and reduced burden on clinical staff (35, 36). Self-collection of rectal and pharyngeal specimens can also expand the settings in which testing can occur, creating opportunities for alternative testing venues such as home- and Internet-based testing, which might be particularly attractive for younger and adolescent patients (37–39). While some researchers and public health programs have demonstrated the acceptability and feasibility of home- and Internet-based STI testing, there are special considerations for adolescents, such as confidentiality, linkage to treatment and care, partner notification, and cases of potential child sexual abuse (40, 41). Addressing those concerns is critical to improve access to testing in those populations, as adolescents and young adults have the highest prevalence of STIs (42). Future interventions should also look into how to harness those collection methods and technologies to improve screening for *C. trachomatis* and *N. gonorrhoeae* at a population level.

While screening for *C. trachomatis* and *N. gonorrhoeae* pharyngeal and rectal infections is supported in many countries, evidence demonstrating the benefits of screening on a population level is limited. Modeling studies, primarily among MSM on HIV preexposure prophylaxis (PrEP), have shown that increasing the frequency of rectal and pharyngeal screening for *C. trachomatis* and *N. gonorrhoeae* might result in lower incidence of infections (43, 44). However, real-world data demonstrating a reduction in *C. trachomatis* or *N. gonorrhoeae* incidence through routine rectal and pharyngeal screening on a population scale are lacking. The potential benefits of a reduction in infection incidence and the prevention of clinical complications must be weighed against the costs and potential harms associated with the expansion of testing and the increase in antibiotic consumption, raising concerns of antimicrobial resistance, particularly in *N. gonorrhoeae* (45). A key consideration for future research is the evaluation of different testing methods and frequencies in order to establish an evidence base to support the screening recommendations.

Despite the absence of real-world data to support screening for rectal and pharyngeal *C. trachomatis* and *N. gonorrhoeae* as a way to reduce disease incidence, the identification of rectal infections can be an important biomarker for the risk of HIV acquisition (4). Indeed, a benefit from screening for rectal infections includes the opportunity to use the diagnosis as an entry point for patients into HIV prevention and PrEP programs. Therefore, the identification of those infections should prompt clinicians to conduct a clinical risk assessment to determine eligibility for HIV PrEP programs, which play a critical role in HIV prevention strategies (46).

CONCLUSIONS

In summary, the rectum and the pharynx are important anatomic sites of *C. trachomatis* and *N. gonorrhoeae* infections. Screening recommendations for rectal and pharyngeal *C. trachomatis* and *N. gonorrhoeae* infections vary by age, sex, and sexual behavior. NAATs are the mainstay for the detection of those infections due to their high sensitivity and high specificity. Several assays have recently been approved by the FDA for use in rectal and pharyngeal specimens, and others are in the pipeline. Previously, a major barrier to providing such testing was the lack of FDA-cleared tests, but now that has been overcome, clinical microbiology laboratories must still perform assay verification for these specimen types, which typically involves a minimum of 20 positive and 50 negative specimens for FDA-cleared assays (47). Laboratories can work with assay manufacturers, the Association of

Public Health Laboratories, the CDC, or other reference laboratories that have previously verified a NAAT for use in rectal and pharyngeal specimens to obtain panels of samples for verification testing (48). Given the availability of several FDA-cleared assays for detecting *C. trachomatis* and *N. gonorrhoeae* in rectal and pharyngeal specimens, clinical microbiology laboratories should offer testing in these specimen types as part of comprehensive diagnostic testing for STIs.

While many point-of-care tests are available for detecting urogenital *C. trachomatis* and *N. gonorrhoeae* infections, only one non-CLIA-waived point-of-care assay is currently approved for use with rectal and pharyngeal specimens. Expanding screening venues and using self-collected rectal and pharyngeal specimens can help to increase access and uptake of testing. Further research into the potential benefits and harms associated with increased screening for rectal and pharyngeal *C. trachomatis* and *N. gonorrhoeae* infections on a population level is needed.

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