Diagnostic Testing of Common Sexually Transmitted Infections

Policy Number: AHS – G2157 – Diagnostic Testing of Common Sexually Transmitted Infections	Prior Policy Name and Number, as applicable: Portions of this policy replaces portions of M2097- Identification of Microorganisms using Nucleic Acid Probes
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I. Policy Description

Sexually transmitted infections (STIs), often referred to as sexually transmitted diseases or STDs, include a variety of pathogenic bacteria, virus, and other microorganisms that are spread through sexual contact and can cause a multitude of complications if left untreated. Chlamydia and gonorrhea, caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, respectively, have high rates of occurrence in the United States and can cause pelvic inflammatory disease (PID), infertility, and pregnancy complications. The causative agent of syphilis is *Treponema pallidum*; if left untreated, syphilis can lead to serious cardiac and neurological conditions (Ghanem & Tuddenham, 2020). Trichmoniasis is a common genitourinary infection caused by *Trichomonas vaginalis*. This infection is the most common cause of vaginal complaints, but other areas such as the prostate and bladder may be affected (Sobel, 2020). Human papillomavirus (HPV) is a double-stranded DNA virus that can be sexually transmitted and is associated with cervical cancer, vulvar/vaginal cancer, anal cancer, oropharyngeal cancer, penile cancer, and both genital and nongenital warts. "Globally, anogenital HPV is the most common sexually transmitted infection" with an estimated 80% of sexually active adults exposed to it at least once in their lifetime (Palefsky, 2019). Herpes simplex virus (HSV) is a common STI where many individuals are asymptomatic. HSV infection has been linked to an increased risk of other infections, including HIV, and in rare cases, can also result in HSV meningitis or proctitis (Albrecht, 2018). In general, risk factors for STIs can include both behavioral elements, such as multiple sex partners, working in a sex trade, and inconsistent use of condoms when in nonmonogamous relationships as well as demographic risks, including men who have sex with men (MSM), prior STI diagnosis, admission to correctional facilities, and lower socioeconomic status (Ghanem & Tuddenham, 2017).

This policy is limited to testing for *C. trachomatis*, *N. gonorrhoeae*, *T. pallidum*, *T. vaginalis*, HSV, and HPV. The following conditions and/or tests are discussed in the corresponding policies:

- HIV: AHS-M2093 HIV Genotyping and Phenotyping; AHS-M2116 Plasma HIV-1 RNA Quantification for HIV-1 Infection
- Hepatitis C: AHS-G2036
- Preventive Screening: AHS-G2009

- Pediatric Preventive Screening: AHS-G2042

- Prenatal Screening: AHS-G2035
- Cervical Cancer Screening: AHS-G2002

- Pathogen Panel Testing: AHS-G2149

II. Related Policies

Policy Number	Policy Title
AHS-G2002	Cervical Cancer Screening
AHS-G2009	Preventive Screening in Adults
AHS-G2035	Prenatal Screening
AHS-G2036	Hepatitis C
AHS-G2042	Pediatric Preventive Screening
AHS-G2149	Pathogen Panel Testing
AHS-M2057	Diagnosis of Vaginitis Including Multi-Target PCR Testing
AHS-M2093	HIV Genotyping and Phenotyping
AHS-M2116	Plasma HIV-1 RNA Quantification For HIV-1 Infection

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Medical Policy Statements do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination.

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. If there is a conflict between this Policy and any relevant, applicable government policy [e.g. National Coverage Determinations (NCDs) for Medicare] for a particular member, then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

1. Testing for syphilis infection **MEETS COVERAGE CRITERIA** in the following situations:

    a. For any asymptomatic person in a high-risk category* (See Note 1), once a year assessment using either a "standard" or "reverse" algorithm that includes initial and confirmatory tests for any initial positive test such as:

        i. Treponemal Ig test AND ii.

        Nontreponemal test; OR

    b. Once every three months for HIV-positive men or MSM; OR

    c. As part of a pregnancy screening; OR

    d. For diagnosis of any person presenting with signs and/or symptoms of a syphilis infection* (See Note 2); OR

    e. A nontreponemal test as test of cure of treatment of a positive syphilis infection.

2. Screening for syphilis of asymptomatic individuals NOT belonging to a high-risk category* (See Note 1) **DOES NOT MEET COVERAGE CRITERIA** except for the following:

    a. As part of newborn screening; OR

    b. As part of a pregnancy screening; OR

    c. As part of follow-up of victim of sexual assault.

3. Testing for syphilis using PCR or NAAT **DOES NOT MEET COVERAGE CRITERIA**.

4. Nucleic acid amplification tests (NAATs) for chlamydia **MEETS COVERAGE CRITERIA** in the following situations:

    a. Once a year assessment for any asymptomatic person in a high-risk category* (See Note 3); OR

    b. As part of a pregnancy screening; OR

    c. For diagnosis of any person presenting with signs and/or symptoms of a chlamydial infection* (See Note 4); OR

    d. For diagnosis of any person with suspected lymphogranuloma venereum (LGV); OR

    e. As test of cure of treatment at least three months after initial chlamydial diagnosis.

5. Screening for chlamydia of asymptomatic individuals NOT belonging to a high-risk category* (See Note 3) **DOES NOT MEET COVERAGE CRITERIA** except for the following:

a. As part of newborn screening; OR

b. As part of pregnancy screening; OR

c. As part of follow-up of victim of sexual assault.

6. Serology testing for chlamydia or lymphogranuloma venereum (LGV) **DOES NOT MEET COVERAGE CRITERIA**.

7. Nucleic acid amplification tests (NAATs) for gonorrhea **MEETS COVERAGE CRITERIA** in the following situations:

   a. Once a year assessment for any asymptomatic person in a high-risk category* (See Note 3); OR

   b. As part of a pregnancy screening; OR
   c. For diagnosis of any person presenting with signs and/or symptoms of a gonorrheal infection* (See Note 5); OR

   d. As test of cure of treatment.

8. Culture testing for *N. gonorrhoeae* **MEETS COVERAGE CRITERIA** for testing antimicrobial susceptibility if patient does not respond to initial treatment.

9. Screening for gonorrhea of asymptomatic individuals NOT belonging to a high-risk category* (See Note 3) **DOES NOT MEET COVERAGE CRITERIA** except for the following:

   a. As part of newborn screening; OR

   b. As part of pregnancy screening; OR

   c. As part of follow-up of victim of sexual assault.

10. Nucleic acid amplification tests (NAATs) for herpes simplex virus-1 or herpes simplex virus-2 (HSV-1 and HSV-2, respectively) in patients with active genital ulcers **MEETS COVERAGE CRITERIA**.

11. Using immunoassay testing for herpes simplex virus-1 (HSV-1), herpes simplex virus2 (HSV-2), and/or herpes simplex (non-specific type test) **DOES NOT MEET COVERAGE CRITERIA**.

12. Screening for herpes simplex virus-1 or herpes simplex virus-2 (HSV-1 and HSV-2, respectively) in asymptomatic patients **DOES NOT MEET COVERAGE CRITERIA**.

13. Testing for human papillomavirus (HPV) **MEETS COVERAGE CRITERIA** in the following:

a. Immunohistochemistry testing for p16 or NAAT testing for HPV, including testing for highrisk types HPV-16 and HPV-18, in the diagnosis and/or assessment of cancer or cancer therapy; OR

b. For women aged 30 to 65 years, once every five years as part of a cervical screening as indicated in AHS-G2002.

14. Screening for HPV **DOES NOT MEET COVERAGE CRITERIA** in the following situations:

a. Screening for oncogenic high-risk types, such as HPV-16 and HPV-18, as part of a general sexually transmitted disease (STD) or sexually transmitted infection (STI) screening process or panel for asymptomatic patients; OR

b. As part of diagnosis of anogenital warts; OR

c. Screening for low-risk types of HPV; OR
d. In the general population either as part of a panel of tests or as an individual NAAT to determine HPV status.

15. Nucleic acid amplification tests (NAATs) or PCR-based testing for *T. vaginalis* **MEETS COVERAGE CRITERIA** in the following situations:

a. Symptomatic individuals* (See Note 6)

b. Asymptomatic individuals belonging to a high-risk group

i. Concurrent STI or History of STIs ii. Individuals in high

prevalence settings, such as STI clinics iii. Individuals who

exchange sex for payment

c. NOTE: For further guidance for individuals with vaginitis, please refer to policy AHS-2057 Diagnosis of Vaginitis Including Multi-Target PCR Testing.

16. Rapid identification of *Trichomonas* by enzyme immunoassay **DOES NOT MEET COVERAGE CRITERIA**.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

17. Using nucleic acid testing to quantify the following microorganisms **DOES NOT MEET COVERAGE CRITERIA**:

a. Chlamydia trachomatis

b. Neisseria gonorrhoeae

c. Herpes Simplex Virus-1

d. Herpes Simplex Virus-2

e. Human Papillomavirus

f. *Treponema pallidum*

g. *Trichomonas vaginalis*

NOTE 1: <u>High-risk for Syphilis (Cantor, Pappas, Daeges, & Nelson, 2016; CDC, 2017c)</u>:

- Sexually active men who have sex with men (MSM)
- Sexually active HIV-positive status
- Having a sexual partner recently diagnosed with an STI
- Exchanging sex for money or drugs
- Individuals in adult correctional facilities

NOTE 2: <u>Signs and Symptoms of a Syphilis Infection (CDC, 2017c)</u>

- Chancre
- Skin rash and/or mucous membrane lesions in mouth, vagina, anus, hands, and feet
- Condyloma lata
- Secondary symptomology can include fever, fatigue, sore throat, swollen lymph nodes, weight loss, muscle aches, headache, and hair loss

NOTE 3: <u>High-risk for Chlamydia and/or Gonorrhea (CDC, 2016a, 2019b; LeFevre, 2014)</u>:

- Sexually active men who have sex with men (MSM)
- Sexually active HIV-positive status
- Sexually active women under the age of 25
- Women age 25 or over who have multiple sexual partners
- Having a sexual partner recently diagnosed with an STI
- Previous or concurrent STI
- Exchanging sex for money or drugs

NOTE 4: <u>Signs and Symptoms of a Chlamydia Infection (CDC, 2016a):</u>

- Genital symptoms, including “discharge, burning during urination, unusual sores, or rash”

- Pelvic Inflammatory Disease, including "symptoms of abdominal and/or pelvic pain, along with signs of cervical motion tenderness, and uterine or adnexal tenderness on examination" • Urethritis
- Pyuria
- Dysuria
- Increase in frequency in urination
- Epididymitis (with or without symptomatic urethritis) in men
- Proctitis
- Sexually acquired chlamydial conjunctivitis

NOTE 5: <u>Signs and Symptoms of Gonorrhea (CDC, 2016b):</u>

- Dysuria
- Urethral infection
- Urethral or vaginal discharge
- Epididymitis (Testicular or scrotal pain)
- Rectal infection symptoms include anal itching, discharge, rectal bleeding, and painful bowel movements

NOTE 6: <u>Signs and Symptoms of Trichomoniasis (CDC, 2015, 2020):</u>

- Vaginal or penile discharge
- Itching, burning sensation, or soreness of the genitalia
- Discomfort or burning sensation during/after urination and/or ejaculation
- Urethritis
- Epididymitis
- Prostatitis

IV. Scientific Background

Chlamydia

Chlamydia, caused by the bacterium *Chlamydia trachomatis*, is usually an asymptomatic sexually transmitted infection that can be passed to a newborn from an infected mother, potentially resulting in conjunctivitis and/or pneumonia. Symptomatic infections can include cervicitis, pelvic

inflammatory disease (PID), and Fitzhugh-Curtis syndrome in women as well as epididymitis, prostatitis, and reactive arthritis triad in men. Both men and women can have proctitis, urethritis, conjunctivitis, pharyngitis, and genital lymphogranuloma venereum as a result of a chlamydial infection. Nucleic acid amplification testing (NAAT) for chlamydia is the gold standard due to high specificity and sensitivity instead of using culture testing, microscopy, or antigen detection (Hsu, 2019). In the U.S. alone, in 2018, over 1.7 million cases of chlamydia were reported to the CDC, but the CDC estimates that 2.86 million chlamydial infections occur annually (CDC, 2016a). This underreporting is due to individuals who are asymptomatic and, therefore, do not seek treatment. Highest prevalence occurs among men who have sex with men (MSM) and young people. "It is estimated that 1 in 20 sexually active young women aged 14-24 years has chlamydia" (CDC, 2016a).

Gonorrhea

Gonorrhea is a sexually transmitted infection caused by the bacterium *Neisseria gonorrhoeae*. A gonorrheal infection can cause many of the same complications as chlamydia, including PID, cervicitis, and Fitzhugh-Curtis syndrome in women and epididymitis in men. Urethritis, pharyngitis, and proctitis can also occur; in fact, "*N. gonorrhoeae* can be isolated from the urethra in up to 90 percent of women with gonococcal cervicitis" (Ghanem, 2018). Like chlamydia, if left untreated, gonorrhea can be spread from mother to newborn, resulting in conjunctivitis. NAAT is the best method to diagnose gonorrhea, but culture testing is still used to determine antimicrobial susceptibility due to an increase in antibiotic resistance (Bignell & Unemo, 2013). In 2016, the CDC reported an 18.5% increase since 2015 in the number of cases of gonorrhea reported in the United States (CDC, 2017b). The CDC also reported 583,405 new cases of gonorrhea in the United States in 2018 (CDC, 2019b).

Syphilis

Syphilis is caused by the bacterium *Treponema pallidum*, and it progresses, if left untreated, through various stages—primary, secondary, early-latent, late-latent, and late stage syphilis—until infecting the central nervous system. "Syphilis infection is associated with HIV infection and increases the risk for acquiring or spreading HIV" (Cantor et al., 2016). Worldwide, the median rates of infection in males and females were 17.7 cases per 100,000 and 17.2 cases per 100,000, respectively, according to the World Health Organization. The U.S. has reported an increase in the rate of syphilis between 2000 and 2016, and approximately 90% of the new cases of primary and secondary syphilis during this period occurred in men with 81% occurring in men who have sex with men (MSM). "Of particular concern is the uptick in cases of congenital syphilis that is also being seen, with 15.7 cases per 100,000 live births reported in 2016" (Hicks & Clement, 2020).

Similar to other STIs, syphilis is often asymptomatic. For symptomatic syphilis, the signs and symptoms can vary, depending on the stage of disease. Primary syphilis can have a characteristic chancre, a skin lesion, that is usually painless and often heals even in the absence of treatment. Secondary syphilis occurs weeks to months later and can be manifested by typical immunologic responses, such as fever, lethargy, and so on; adenopathy; rash; alopecia; hepatitis; gastrointestinal abnormalities; and even early symptoms of neurological infection, if left untreated. Later stages of syphilis can include cardiovascular abnormalities and progression of neurological syphilitic infection. Asymptomatic, latent syphilis can also occur; moreover, "pregnant women with latent syphilis can transmit *T. pallidum* to their fetus for up to four years after acquisition" (Hicks & Clement, 2018).

The standard protocol for diagnosing a syphilis infection is to use a two-tiered serological testing algorithm of treponemal testing and nontreponemal testing. Treponemal testing is typically more complex than the latter, and they both rely upon the detection of specific treponemal antigens using enzyme immunoassay (EIA), particle agglutination assay, fluorescence, or chemiluminescence immunoassay (CIA). Nontreponemal testing methods, including the rapid plasma reagin test (RPR) and the venereal disease research laboratory (VDRL) test, "are based upon the reactivity of serum from infected patients to a cardiolipin-cholesterol-lecithin antigen" (Hicks & Clement, 2019). Rapid serological testing using darkfield microscopy is not as universally used due to complexity and cost. NAAT has not been FDA-approved at this time and is not typically performed for genital syphilis. "There is no internationally approved PCR for *T. pallidum* and accordingly, it is crucial to select a strictly validated method and always use it with appropriate quality controls" (Janier et al., 2014).

Herpes Simplex Virus (HSV)

Herpes Simplex Virus-2 (HSV-2) is the common cause of most of genital herpes simplex infections worldwide with the CDC estimating that 50 million people in the U.S. were infected with HSV-2 in 2015 (Workowski & Bolan, 2015). More than 770,000 people in the U.S. are infected each year with genital herpes; moreover, HSV-1 genital herpes is increasing in recent years. This trend is believed to be due to a decline in childhood oral HSV-1 infections that in the past increased immune resistance to genital HSV-1 infections (CDC, 2017a). Primary genital herpes infections can present with genital ulcers as well as other immunological responses, such as fever and lymphadenopathy; however, for some people, a primary genital herpes infection is asymptomatic. Nonprimary infections occur when a patient acquires HSV-1 with pre-existing HSV-2 antibodies or vice versa. Recurrent infections can be either symptomatic or asymptomatic, which can be referred as subclinical. A minority of HSV-positive patients can also present with meningitis and/or proctitis (Albrecht, 2017). Vertical transmission from mother to newborn can occur during delivery, especially if the mother acquires a primary infection near the end of the pregnancy. This vertical transmission can occur even if the mother is asymptomatic (Riley & Wald, 2020). Diagnosis of genital herpes infection can be performed by viral culture, NAAT, and serological testing. "Cell culture and PCR-based testing are the preferred tests for a patient presenting with active lesions, although PCR-based testing has the greatest overall sensitivity and specificity" (Albrecht, 2017).

Human Papillomavirus (HPV)

Anogenital HPV infection is the most common STI worldwide with an estimation that "at least 80 percent of sexually active women and men are exposed to HPV once in their lifetime. However, many experts believe that virtually all sexually active adults have been infected by HPV…"(Palefsky, 2018). This is due to the large number of different types of HPV known to infect the genital tract—at least 40 characterized to date—and the transitory nature of HPV infections. HPV is associated with a variety of cancers, including anal, penile, vulvar, vaginal, and oropharyngeal cancer; moreover, the carcinogenic effect of an HPV infection can be years after the initial diagnosis of HPV. Multiple HPV vaccinations have been approved for use in the U.S., and the CDC recommends vaccination for HPV for all children ages 11 or 12 (CDC, 2019a). HPV can be detected from swab samples and can be included in many routine cervical exams. High-risk oncogenic HPV testing is commercially available (Feldman & Crum, 2020).

Trichomoniasis

Trichomoniasis is a common genitourinary infection caused by *Trichomonas vaginalis*. This infection is the most common cause of vaginal complaints, but other areas such as the prostate and bladder may be affected. Affected individuals may experience symptoms such as discharge or dysuria. However, up to 85% of women and over 75% of men are asymptomatic. Microscopy is typically the first-line test used for diagnostics as it is useful for evaluation of discharge, and a confirmatory nucleic acid amplification test (NAAT) may be performed if microscopy results are inconclusive. In men, a culture (with up to 95% sensitivity and >95% specificity) or NAAT are usually performed for diagnosis (Sobel, 2019).

Analytical Validity

A 2005 study by Cook and colleagues (Cook, Hutchison, Ostergaard, Braithwaite, & Ness, 2005) reviewed the validity of NAAT for chlamydia and gonorrhea from urine samples as compared to swabs obtained directly from either the cervix or urethra. They reviewed 29 different studies and only included studies using collections of samples obtained from two anatomic sites. Each test required either a secondary culture confirmation or a secondary NAAT-based confirmation. Over 20,000 different patients were included in the pooled study, and three different NAAT assays were monitored—polymerase chain reaction (PCR), transcription-mediated amplification (TMA), and strand displacement amplification (SDA). "The pooled study specificities of each of the 3 assays exceeded 97% when urine samples were tested, for both chlamydial infection and gonorrhea and in both men and women." The use of PCR for gonorrheal testing, though, from female urine samples had only 55.6% specificity. The authors concluded the following: "Results of nucleic acid amplification tests for *C. trachomatis* on urine samples are nearly identical to those obtained on samples collected directly from the cervix or urethra. Although all 3 assays can also be used to test for *N. gonorrhoeae*, the sensitivity of the polymerase chain reaction assay in women is too low to recommend its routine use to test for gonorrhea in urine specimens (Cook et al., 2005)."

Due to an increase in demand for enzyme immunoassay-based testing of syphilis, Wong et al. (2011) evaluated the validity of such testing—using the Trep-Sure EIA test—to that of the documented Venereal Disease Research Laboratory (VDRL) test and Treponema pallidum particle agglutination (TPPA) assay. Their research included 674 samples. The EIA-based test had a sensitivity of 98.0% and a specificity of 98.6% (Cantor et al., 2016). The authors conclude that "an IgM/IgG sensitive EIA would be an effective alternative to VDRL for syphilis screening" (Wong et al., 2011). An earlier study using another EIA-based assay, the Trep-Check IgG EIA test, conducted at the National Microbiology Laboratory of Canada (Tsang, Martin, Lau, & Sawatzky, 2007) did not report as positive results as the Wong study. This research consisted of 604 samples submitted from local or provincial hospitals for confirmation of local testing. Their findings were that the Trep-Check IgG EIA had a sensitivity of 85.3% and specificity of 95.6%, but they also report a positive predictive value of 53.7% (Tsang et al., 2007) as compared to the positive predictive value of 98.4% of the Trep-Sure EIA test (Cantor et al., 2016; Wong et al., 2011). These results can be compared to the published results of the accuracy of the TPPA assay of 87.1% sensitivity, 100% specificity, and 100% positive predictive value—albeit in a smaller sample size (n = 198) (Cantor et al., 2016; Juarez-Figueroa, Uribe-Salas, Garcia-Cisneros, Olamendi-Portugal, & Conde-Glez, 2007).

The US Preventive Services Task Force (USPSTF) conducted a systematic review of the use of serologic screening for genital herpes and published their findings in 2016 (Feltner, Grodensky, Ebel, & et al.,

2016). Their extensive review consisted of 17 different studies, ranging from 24 to 3,290 participants, in 19 different publications. Reviewing only the serological testing of HSV-2, they note that the "pooled estimates of sensitivity and specificity of the most commonly used test at the manufacturer's cutpoint were 99% (95% CI, 97%-100%) and 81% (95% CI, 68%-98%), respectively." However, they also note that "use of this test at the manufacturer's cutpoint in a population of 100 000 with a prevalence of HSV-2 of 16% (the seroprevalence in US adults with unknown symptom status) would result in 15 840 true-positive results and 15,960 false-positive results (positive predive value, 50%)." They note the potential psychosocial harm due to false-positive results. The authors conclude, "Serologic screening for genital herpes is associate with a high rate of false-positive test results and psychosocial harms" (Feltner et al., 2016).

The ATHENA study conducted in 2008-2009 and published in Lancet in 2011 consisted of more than 40,000 women in the U.S. aged 25 or over in 61 different clinical centers. The goal was to assess highrisk HPV16 and HPV18 testing versus traditional methods. Their results show that "in women who had colposcopy, the Cobas HPV test was more sensitive than liquid-based cytology for detection of CIN3 [cervical intraepithelial neoplasia grade 3] or worse" with 92.0% versus 53.3% for liquid cytology. "Addition of liquid-based cytology to HPV testing increased sensitivity for CIN3 or worse to 96.7%...but increased the number of screen positives by 35.2%." The authors conclude, "HPV testing with separate HPV16 and HPV18 detection could provide an alternative, more sensitive, and efficient strategy for cervical cancer screening than do methods based solely on cytology (Castle et al., 2011)." Guenat and colleagues report a coefficient of variation of less than 8% for repeatability and reproducibility when using the Novaprep HQ+ medium in liquid-based cytology for HPV (Guenat, Launay, Riethmuller, Mougin, & Pretet, 2016). Another study comparing the validity of using urine samples in comparison with cervical samples for monitoring HPV in women over the age of 30 shows that the sensitivity of the urine testing varies considerably depending on the NAAT assay used. The multiplex type-specific PCR (E7-MPG) assay had a sensitivity of 80% and specificity of only 61% whereas the GP5+/6+ PCR assay resulted in 58% and 89%, respectively, for sensitivity and specificity as compared to the gold standard cervical swabs (Tshomo et al., 2017).

A 2017 study by Gaydos et al. (2017) compared the efficacy of rapid and point-of-care tests for *T. vaginalis* in women and men. The tests reviewed in the study included the OSOM lateral flow test, the GeneXpert test, the AmpliVue test, and the Solana test. The authors report a sensitivity of 83–86% for the OSOM test. They note that "AmpliVue demonstrated a sensitivity for vaginal swabs of 100% compared with wet preparation/culture and 90.7% compared with NAATs. Solana demonstrated a sensitivity of 98.6%–100% for vaginal swabs and 92.9%–98% for female urines, compared with wet preparation/culture. Compared with other NAATs, the sensitivity for Solana was 89.7% for swabs and 100% for urine… The sensitivity [of the GeneXpert TV test] compared with wet preparation/culture for self-collected vaginal swabs was 96.4%, 98.9% for endocervical specimens and 98.4% for female urine. For men, sensitivity for urines was excellent (97.2%). The specificity for all assays was excellent (Gaydos et al., 2017)."

A study by Golden et al. (2019) compared the sensitivity of syphilis serological testing using the rapid plasma reagin (RPR) test and an experimental 23S rRNA *Treponema pallidum* real-time transcriptionmediated amplification (TMA) assay. This study included 545 men who have sex with men (MSM); a total of 506 pharyngeal specimens and 410 rectal specimens were provided for this study. Twentytwo men were diagnosed with syphilis based on serological testing results; further, two more men were diagnosed based on TMA testing results. The authors report that "At least 1 specimen

was TMA positive for 12 of 24 men with syphilis (sensitivity, 50% [95% confidence interval [CI], 29 to 71%]). RPR testing and clinical diagnosis were 92% sensitive (95% CI, 73 to 99%) in identifying infected men" (Golden et al., 2019). A combinatory approach of mucosal TMA testing and serological testing may improve the sensitivity of syphilis screening.

Clinical Validity and Utility

A 2017 review of point-of-care tests (POCTs) versus near-patient NAAT for chlamydia reviewed 11 different studies consisting of a combined total of more than 13,000 patients. The pooled results show that POCTs have a sensitivity of only 53%, 37%, and 63% for cervical swabs, vaginal swabs, and male urine, respectively, but that the specificity for each ranged from 97-99%. The near-patient NAAT has a sensitivity of >98% regardless of sample with a specificity of 99.4%. "The systematic reviews show that antigen detection POCTs for CT [*C. trachomatis*], although easy to use, lacked sufficient sensitivity to be recommended as a screening test. A near-patient NAAT shows acceptable performance as a screening or diagnostic test but requires electricity, takes 90 min and is costly (Kelly et al., 2017)." Likewise, a review of five POCTs and one near-patient NAAT for gonorrhea in 2017 show that POTC immunochromatographic tests and optical immunoassays had sensitivities ranging from 12.5% to 70% compared to laboratory NAAT for cervical and vaginal swab samples. The specificities of the nearpatient NAATs were >99.8% with sensitivities >95% (Guy et al., 2017).

A 2018 review of laboratory testing for *T. pallidum* in Australia (Brischetto, Gassiep, Whiley, & Norton, 2018) compared the clinical value of PCR testing for syphilis as compared to the traditional serological testing using RPR, agglutination, and/or chemiluminescence immunoassay (CMIA). This review covered all testing at the Australian lab from 2010 to 2017. They show that 19% of PCR results were positive for syphilis with 97% of those patients also showing positive serological results. The *T. pallidum* PCR had a sensitivity of 68% and specificity of 99% as compared to the serology testing sensitivity of 97% and 88% specificity. "Our results show that most patients with positive *T. pallidum* PCR results also had positive syphilis serology. Therefore, *T. pallidum* PCR adds little clinical value over serology for the diagnosis of syphilis in certain clinical settings (Brischetto et al., 2018)." A 2015 Chinese study (Zhiyan et al., 2015) does show that the CMIA screening is not as specific as the TPPA agglutination assay for syphilis with 18 of the 149 CMIA-positive samples being false-positive results.

The 2016 USPSTF review of genital herpes serological testing (Feltner et al., 2016) included a review of the HerpeSelect serological test consisting of the data from ten studies with a combined total of 6537 participants. The pooled, combined results show a sensitivity of 99% and specificity of 81%. Four additional studies they reviewed used the biokit HSV-2 Rapid Test assay. These studies had a combined total of 1512 participants. The sensitivity is considerably lower (84%), but the specificity was higher than the HerpeSelect assay (95%).

A study by Liu and associates (Liu et al., 2014) evaluated the clinical performance of the QuantiVirus HPV E6/E7 mRNA with respect to identifying ≥Grade 2 cervical intraepithelial neoplasia. Approximately 40.3% of the 335 female patients tested positive for high-risk HPV. They note that "the positivity rate of HPV E6/E7 mRNA increased with the severity of cytological and histological evaluation…a high specificity and a low positivity rate of E6/E7 mRNA testing as a triage test in HPV DNA-positive women can be translated into a low referral for colposcopy (Liu et al., 2014)." Another study of the QuantiVirus system in 2017 (Yao et al., 2017) of 404 HPV-positive women show no statistical difference between QuantiVirus and cytological testing in sensitivity, specificity, positive predictive value, and negative predictive value for predicting high-grade squamous intraepithelial

lesion (HSIL). "HPV E6/E7 mRNA detection in cervical exfoliated cells shows the same performance as Pap triage for HSIL identification for HPV-positive women. Detection of HPV E6/E7 mRNA may be used as a new triage option for HPV-positive women (Yao et al., 2017)." A review by Arbyn and colleagues concerning the efficacy of repeat cytology versus HPV testing for atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSIL) demonstrated that the pooled sensitivity of the Hybrid Capture 2 (HC2) assay for the high-risk HPV types was significantly higher than performing repeat cytology (relative sensitivity of 1.27 and 1.23, respectively) for detecting CIN2+ but was significantly lower than repeat cytology for LSIL. "HPV-triage with HC2 can be recommended to triage women with ASCUS because it has higher accuracy…than repeat cytology. When triaging women with LSIL, an HC2 test yields a significantly higher sensitivity, but a significantly lower specificity, compared to repeat cytology. Therefore, practice recommendations for management of women with LSIL should be balanced, taking local circumstances into account (Arbyn et al., 2013)."

Schwebke et al. (2018) evaluated the rates of *Trichomonas vaginalis* infections in a large high-risk population. The study included 77740 women and 12604 men from family planning and/or sexually transmitted disease clinics, and a nucleic acid amplification test was used. The overall rate of trichomonas was found to be 11.3% in the female cohort and 6.1% in the male cohort. The rates of infection increased with age in both genders, with females under 18 reaching a 6.3% rate and females above 50 reaching a 16% rate. For males under 18, the rate of infection was 1.2% and for males over 50, the rate was 11.5% (Schwebke et al., 2018).

A study by Gaydos et al. (2019) showed that, for women in the emergency department (ED), the use of rapid diagnostic tests for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections can improve clinical management. This randomized clinical trial was composed of 254 women undergoing pelvic examinations for both *C. trachomatis* and *N. gonorrhoeae* testing; the women were split into control and rapid test groups. For the rapid test group, the GeneXpert rapid test was used. The authors report that "Undertreatment for both *C trachomatis* and *N gonorrhoeae* in the ED was 0% for the rapid test group and 43.8% for the control standard-of-care group. Clinicians overtreated 46.5% of uninfected standard-of-care control patients for *C trachomatis* compared with 23.1% of uninfected rapid test patients. For patients uninfected with *N gonorrhoeae*, clinicians overtreated 46.7% of standard-ofcare control patients compared with 25.4% of rapid test patients" (Gaydos et al., 2019). These results show that rapid testing of *C. trachomatis* and *N. gonorrhoeae* led to a significant reduction in overtreatment compared to the control group.

V. Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN) (NCCN, 2019, 2020)

Anal Carcinoma (NCCN, 2019a, 2020b): HPV, especially high-risk types HPV-16 and HPV-18, are linked to anal carcinoma. The NCCN refers to a study that detected HPV in 84% of anal carcinoma samples and 0% in rectal cancer samples, and they state that "the prevalence of HPV-16/18 to be 72% in patients with invasive anal cancer." Precursor high-grade anal intraepithelial neoplasia (AIN) "can be identified by cytology, HPV testing, digital rectal examination (DRE), high-resolution anoscopy, and/or biopsy." They also state that "recent data suggest that HPV- and/or p16-positivity are prognostic for improved OS [overall survival] in patients with anal carcinoma." For females, the NCCN also recommends a gynecologic examination due to the link between HPV and anal carcinoma.

Cervical Cancer (NCCN, 2019b, 2020c): "Persistent human papillomavirus (HPV) infection is the most important factor in the development of cervical cancer. The incidence of cervical cancer appears to be related to the prevalence of HPV in the population…. Screening methods using HPV testing may increase detection of adenocarcinoma." The NCCN lists chronic, persistent HPV infection along with persistently abnormal Pap tests as criteria to be considered for women contemplating hysterectomy after the completion of childbearing.

Head and Neck Cancers (NCCN, 2019c, 2020d): The NCCN in the Head and Neck Cancers guidelines now specifically states, "Tumor human papillomavirus (HPV) testing by p16 immunohistochemistry (IHC) required" in their workup for cancer of the oropharynx because the p16 status dictates the treatment options to be considered (per the ORPH-1 workup). This version of the guidelines also includes a page on the "Principles of P16 Testing for HPV-Mediated Oropharyngeal Cancer" where they state the following:

- "P16 expression is highly correlated with HPV status and prognosis and is widely available."
- "A few HPV testing options are available for use in the clinical setting. Expression of p16 as detected by IHC is a widely available surrogate biomarker that has very good agreement with HPV status as determined by the gold standard of HPV E6/E7 mRNA expression. Other tests include HPV detection through PCR and in situ hybridization (ISH).
- "Sensitivity of IHC staining for p16 and PCR-based assay is high, although specificity is highest for ISH."
- "Due to variations in sensitivity and specificity values of testing options, multiple methods may be used in combination for HPV detection, but HPV detection through PCR and ISH may provide additional sensitivity for the former and specificity for the latter in the case of an equivocal p16 or unclear clinical scenario."
- "Sufficient pathologic material for HPV testing can be obtained through FNA."
- "A small proportion of tumors at non-oropharyngeal sites (eg, paranasal sinus, oral cavity, larynx) are HPV-related. However, given the small proportion and lack of consistent evidence in support of prognostic significance, routine HPV testing or p16 [testing] of non-oropharyngeal cancers is not recommended."
- "Guidelines for testing are available from the College of American Pathologists."

Occult Primary Cancers (NCCN, 2020a): The NCCN now lists HPV to be tested for Occult Primary cancers. The NCCN also states that for squamous cell carcinoma with a clinical presentation in the head and neck nodes, "Check results of p 16 immunohistochemistry/HPV in situ hybridization and EBV in situ hybridization; positive results can help localize primary site." Further, the guidelines note that HPV can be used as a potential immunohistochemistry marker for unknown primary cancers, including tumors identified in the cervix, vulva, vagina, penis, anal, oropharynx; a nuclear (DNA ISH) or nuclear/cytoplasmic (RNA ISH) staining pattern is recommended (NCCN, 2020a).

Penile Cancer (NCCN, 2019d, 2020e): "Overall, about 45% to 80% of penile cancers are related to HPV, with a strong correlation with types 16, 6 and 18." Discerning whether a penile cancer lesion is infected with HPV is important for laser ablation therapy as noted in the section titled "Principles of Penile Organ-Sparing Approaches."

Vulvar Cancer (NCCN, 2019e, 2020f): "Risk factors for the development of vulvar neoplasia include increasing age, infection with human papillomavirus (HPV), cigarette smoking, inflammatory

conditions affecting the vulva, and immunodeficiency…. Usual-type VIN [vulvar intraepithelial neoplasia] was linked to persistent infection with carcinogenic strains of HPV, while differentiated VIN was commonly associated with vulvar dermatologic conditions such as lichen sclerosus. In 2015, the ISVVD updated the description to 3 classes of vulvar lesions: 1) low-grade squamous intraepithelial lesion (LSIL) due to flat condyloma or HPV effect; 2) high-grade squamous intraepithelial lesions (HSIL, formerly considered usual-type VIN); and 3) differentiated VIN." The NCCN notes that 80-90% of HSIL cases have HPV infections and that between 30%-69% of all vulvar cancers are believed to be "attributable to HPV infection." In the "Diagnosis and Workup" section, they state, "Appropriate patients should receive smoking cessation counseling and HPV testing." The guidelines also note for the surveillance of vulvar cancer: "cervical/vaginal cytology screening as indicated for the detection of lower genital tract neoplasia (may include HPV testing)" (NCCN, 2020f).

2014, 2016 U.S. Preventive Services Task Force (USPSTF) (Cantor et al., 2016; Feltner et al., 2016; LeFevre, 2014; Moyer, 2014)

Screening for Chlamydia and Gonorrhea (LeFevre, 2014): The USPSTF recommends (Grade B) to screen for chlamydia and gonorrhea in "sexually active females aged 24 years or younger and in older women who are at increased risk for infection." They also conclude (an "I" statement) "that the current evidence is insufficient to assess the balance of benefits and harms of screening for chlamydia and gonorrhea in men." Besides age, "other risk factors for infection include having a new sex partner, more than 1 sex partner, a sex partner with concurrent partners, or a sex partner who has an STI; inconsistent condom use among persons who are not in mutually monogamous relationships; previous or coexisting STI; and exchanging sex for money or drugs." They clearly state that both chlamydia and gonorrhea should be tested using NAATs.

Screening for Oral Cancer (Moyer, 2014): Given the link between HPV infection and oral cancers, the USPSTF released their findings concerning the screening of asymptomatic patients. "The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for oral cancer in asymptomatic adults." They also state the following: "Although there is interest in screening for oral HPV infection, medical and dental organizations do not recommend it. Currently, no screening test for oral HPV infection has been approved by the U.S. Food and Drug Administration (FDA). Evaluating the accuracy of tests that detect oral HPV infection is a potentially promising area of research (Moyer, 2014)."

Serological Screening for Genital Herpes (Feltner et al., 2016): HSV-2 is the primary causative agent of genital herpes, and HSV-2 infection during pregnancy can cause fetal morbidity and mortality. Due to its prevalence in the U.S. and the possible consequences of a genital herpes infection, the USPSTF researched the validity and practicality of HSV-2 screening in asymptomatic patients. They conclude that "serologic screening for genital herpes is associated with a high rate of false-positive test results and potential psychosocial harms. Evidence from RCTs [randomized clinical trials] does not establish whether preventive antiviral medication for asymptomatic HSV-2 infection has benefit." Overall, the USPSTF "recommends against routine serologic screening for genital herpes simplex virus (HSV) infection in asymptomatic adolescents and adults, including those who are pregnant."

Screening for Syphilis (Cantor et al., 2016): Previously, in 2004, the USPSTF "recommended routine screening for syphilis in asymptomatic men and nonpregnant women at increased risk of infection (A recommendation) and recommended against routine screening for those not at increased risk (D recommendation)." The previous study did not address the frequency of repeat testing. The current 2016 study adds to the previous recommendations. "Screening HIV-positive men or MSM for syphilis every 3-months is associated with improved syphilis detection. Treponemal or nontreponemal tests are accurate screening tests but require confirmation. Research is needed on the effect of screening on clinical outcomes; effective screening strategies, including reverse sequence screening, in various patient populations; and harms of screening."

Centers for Disease Control and Prevention (CDC) (Papp, Schachter, Gaydos, & Van Der Pol, 2014; Workowski & Bolan, 2015)

Diseases Characterized by Genital, Anal, or Perianal Ulcers: "…all persons who have genital, anal, or perianal ulcers should be evaluated;… Specific evaluation of genital, anal, or perianal ulcers includes 1) syphilis serology, darkfield examination, or PCR testing if available; 2) culture or PCR testing for genital herpes; and 3) serologic testing for type-specific HSV antibody." Later, in the section specifically focused on genital HSV infections, the CDC states, "…the clinical diagnosis of genital herpes should be confirmed by type-specific laboratory testing. Both type-specific virologic and type-specific serologic tests for HSV should be available in clinical settings that provide care to persons with or at risk for STDs." They stress that the patient's prognosis does depend on the type of HSV infection, especially since "recurrences and subclinical shedding are much more frequent for genital HSV-2 infection than for genital HSV-1 infection." Regarding testing, "cell culture and PCR are the preferred HSV tests for persons who seek medical treatment for genital ulcers or other mucocutaneous lesions" (Workowski & Bolan, 2015). NAATs are more sensitive than viral culture testing. On the CDC's detailed fact sheet about genital herpes, they state, "Routine serologic HSV screening of pregnant women is not recommended" (CDC, 2017a).

Syphilis: "Darkfield examinations and tests to detect *T. pallidum* directly from lesion exudate or tissue are the definitive methods for diagnosing early syphilis. Although no *T. pallidum* detection tests are commercially available, some laboratories provide locally developed and validated PCR tests for the detection of *T. pallidum* DNA. A presumptive diagnosis of syphilis requires use of two tests: a nontreponemal test (i.e., Venereal Disease Research Laboratory [VDRL] or Rapid Plasma Reagin [RPR] and a treponemal test (i.e., fluorescent treponemal antibody absorbed [FTA-ABS] tests, the T. pallidum passive particle agglutination [TP-PA] assay, various enzyme immunoassays [EIAs], chemiluminescence immunoassays, immunoblots, or rapid treponemal assays)…Use of only one type of serologic test is insufficient for diagnosis and can result in false-negative results in persons tested during primary syphilis and false-positive results in persons without syphilis." If a patient shows signs and symptoms of neurosyphilis, including "cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense," further testing is required-CSF cell count or protein and a reactive CSF-VDRL (Workowski & Bolan, 2015).

Chlamydial Infections: "Annual screening of all sexually active women aged <25 years is recommended, as is screening of older women at increased risk for infection (e.g., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner

who has a sexually transmitted infection…the screening of sexually active young men should be considered in clinical settings with a high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and STD clinics) or in populations with high burden of infection (e.g., MSM) (Workowski & Bolan, 2015)." Additional guidelines state that "Routine screening is not recommended for men. However, the screening of sexually active young men should be considered in clinical settings with a high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and STD clinics) when resources permit and do not hinder screening efforts in women" (CDC, 2016a).

NAAT testing of first-catch urine or swab specimens is recommended. In the diagnostic considerations section of Chlamydial Infections, the CDC does not address any differences between symptomatic or asymptomatic screening, and they do not mention any specific diagnostic considerations of patients showing signs or symptoms of a chlamydial infection. In the 2014 CDC guide for laboratory testing of chlamydia and gonorrhea, they, too, recommend using NAATs and not the older nonculture or nonNAAT testing methods. "Older nonculture tests and non-NAATs have inferior sensitivity and specificity characteristics and no longer are recommended (Papp et al., 2014)." They do recommend the use of NAATs for extragenital infections, even though such tests have not been FDA-approved, because of their "increased sensitivity, ease of specimen transport and processing" provided that such testing meet CLIA regulatory requirements and any local or state regulations (Papp et al., 2014).

Gonococcal Infections: The CDC recommendation concerning gonococcal screening is similar to that of chlamydia—women aged <25 years and older women and men in high-risk categories. "Screening for gonorrhea in men and older women who are at low risk for infection is not recommended." NAAT allows for best testing of genitourinary infection. However, "culture is available for detection of rectal, oropharyngeal, and conjunctival gonococcal infection, but NAAT is not FDA-cleared for use with these specimens." NAAT testing of rectal and/or oropharyngeal swab specimens can be performed in certain laboratories that have met CLIA requirements even though the testing methodology has not been FDA-approved. Symptomatic men can have testing of urethral secretions performed; however, a negative Gram stain cannot rule out a gonococcal infection, but a positive Gram stain "can be considered diagnostic for infection". Follow-up testing post-treatment for urogenital or rectal gonorrhea is not necessary, but NAAT testing should be performed 14 days after treatment for pharyngeal gonorrhea. Vaginitis is the most common symptom of infection in preadolescent girls (Workowski & Bolan, 2015)."

In the 2014 laboratory guide, the CDC states that "*N. gonorrhoeae* culture capacity is still needed for evaluating suspected cases of treatment failure and monitoring antimicrobial susceptibility." They also state, "*C. trachomatis* and *N. gonorrhoeae* culture capacity might still be needed in instances of child sexual assault in boys and extragenital infections in girls" (Papp et al., 2014).

Human Papillomavirus Infections: Even though testing for oncogenic HPV variants exists, the CDC states, "These tests should not be used for male partners of women with HPV or women aged <25 years, for diagnosis of genital warts, or as a general STD test." For patients showing signs and symptoms of anogenital warts, the CDC states, "HPV testing is not recommended for anogenital wart diagnosis, because test results are not confirmatory and do not guide genital wart management." For cervical screening, "for women aged ≥30 years, screening can include several FDA-approved oncogenic or high-risk HPV (HR-HPV) tests." Between the ages of 30 and 65, women should be screened every

three years (if only doing a Pap test) or every five years if co-testing with a Pap test and an HR-HPV test (Workowski & Bolan, 2015).

The CDC (2019a) also notes that "Routine screening for women aged 21 to 65 years old can prevent cervical cancer"; further, "There are HPV tests that can be used to screen for cervical cancer. These tests are only recommended for screening in women aged 30 years and older. HPV tests are not recommended to screen men, adolescents, or women under the age of 30 years."

Finally, the CDC (2016c) states that "there is currently no approved test for HPV in men. Routine testing (also called 'screening') to check for HPV or HPV-related disease before there are signs or symptom, is not recommended by the CDC for anal, penile, or throat cancers in men in the United States. However, some healthcare providers do offer anal Pap tests to men who may be at increased risk for anal cancer, including men with HIV or men who receive anal sex. If you have symptoms and are concerned about cancer, please see a healthcare provider."

Trichomoniasis infections: The CDC states that diagnostic testing should be done in women with vaginal discharge and that screening "might be considered" for individuals in high-prevalence settings such as STD clinics or asymptomatic high-risk populations such as those with history of STD. The CDC recommends NAATs as the primary diagnostic test. Finally, the CDC states that "Data are insufficient to recommend routine screening, alternative treatment regimens of longer duration, or retesting in men (CDC, 2015)."

International Union Against Sexually Transmitted Infections (IUSTI) (Bignell & Unemo, 2013; H. J. de Vries, Zingoni, Kreuter, Moi, & White, 2015; Gilson, 2019; Janier et al., 2014; Lacey, Woodhall, Wikstrom, & Ross, 2013; Lanjouw et al., 2016; Patel et al., 2017)

The Management of Anogenital Warts (European): "HPV detection or typing does not influence management and is not recommended. Some practitioners use the acetic acid test to diagnose subclinical HPV lesions; its place in diagnosis and management is uncertain (Gilson, 2019)."

The Diagnosis and Treatment of Gonorrhea in Adults (Bignell & Unemo, 2013): NAATs, bacterial culture, and microscopy can be used in the diagnosis of uncomplicated gonorrhea. "No test offers 100% sensitivity and specificity." They do state (with a grade C recommendation) that microscopy can be used for testing symptomatic men, but it is not recommended for use in asymptomatic men, rectal infection, or endocervical infection due to low sensitivity. Culture testing is the only method to use for determining antimicrobial susceptibility, but culture testing is not as sensitive as NAAT. The IUSTI includes the following list for "Indications for testing" (grade C recommendation):

- Symptoms or signs of urethral discharge in men;
- Vaginal discharge with risk factor for STI (age <30 years, new sexual partner);
- Mucopurulent cervicitis;
- Persons diagnosed with any other STI;
- Sexual partner of persons with an STI or PID;
- Acute epididymo-orchitis in a male aged <40 years;
- Acute pelvic inflammatory disease;

- When screening young adults (<25 years of age) for sexually transmitted infections;
- When screening individuals with new or multiple recent sexual partners;
- Purulent conjunctivitis in a neonate or adult; • Mother of a newborn with ophthalmia neonatorum.

***The Management of Lymphogranuloma Venereum (H. J. C. de Vries et al., 2019)*:** Lymphogranuloma venereum (LGV) is a condition caused by chlamydia. The clinical features can vary, depending on the site of inoculation (genital versus rectum) and can include hemorrhagic proctitis, lymphadenopathy, papule or pustule formation, and buboes. Reactive inflammatory responses or physical signs of in infection may include "constitutional symptoms such as low-grade fever, chills, malaise, myalgia, [and] arthralgia." Regarding a diagnosis of lymphogranuloma venereum (LGV), "a sample tested *C. trachomatis* positive with a commercial nucleic acid amplification test (NAAT) platform should be confirmed with an LGV discriminatory NAAT." Further, "For sensitive and specific detection of LGV genovar (L1, L2 and L3, including subvariant)-specific *C. trachomatis* DNA, laboratories are currently recommended to use a two-step procedure (1,B):

- "A commercially available NAAT is used to detect *C. trachomatis* DNA/RNA in suspected clinical samples. These tests cannot discriminate between LGV and non-LGV genovars. Although no commercially available *C. trachomatis* NAATs are FDA-cleared for extragenital specimens, for several NAATs sufficient evidence supports the use of these tests for the detection of C. trachomatis DNA/RNA also in rectal and pharyngeal *C. trachomatis* infections. Some *C. trachomatis* NAAT are CE-labelled for use on rectal and pharyngeal samples in Europe.
- If *C. trachomatis* DNA/RNA is detected, LGV genovar specific *C. trachomatis* DNA should be detected from the same specimen. There are multiplex NAATs for genital ulcerative disease that detect LGV but these have not yet been appropriately evaluated in the context of rectal LGV. Different in-house or laboratory-developed NAATs have been designed and used. The sensitivities of these NAATs are generally lower than the commercially available *C. trachomatis* screening NAAT (H. J. C. de Vries et al., 2019)."

The Management of Syphilis (Janier et al., 2014; Janier et al., 2020): The three stages (primary, secondary, and tertiary) can be overlapping. Primary syphilis begins with appearance of an ulcer (also known as a chancre), usually in the anogenital region with regional lymphadenopathy. "Any anogenital ulcer should be considered syphilitic unless proven otherwise." The secondary stage is characterized by "multisystem involvement due to bacteriaemia, within the first year but may recur up into the second year after infection" and can include skin rash, generalized lymphadenopathy, arthritis, hepatitis, splenomegaly, and kidney dysfunction. Early neurosyphilis can occur in secondary syphilis and can include "meningitis, cranial nerve palsies, auricular and ophthalmic abnormalities (such as uveitis, retinitis, otitis and papillar oedema)." They list the following as conditions of tertiary syphilis:

- "Gummatous syphilis: nodules/plaques or ulcers (skin, mucosae, visceral)"
- "Late neurosyphilis encompasses meningitis, cranial nerve dysfunction, meningovascular syphilis (stroke, myelitis) and parenchymatous neurosyphilis (general paresis, tabes dorsalis)"
- "Cardiovascular syphilis: aortic regurgitation, stenosis of coronary ostia, aortic aneurysm (mainly thoracic)"

The following guidelines were given regarding laboratory testing for *T. pallidum:*

- "Direct detection methods provide definitive diagnosis of syphilis.
- Darkfield examination (DFE) of chancres and erosive cutaneous lesions was the old gold standard method for definitive diagnosis. It gives immediate results. However, the method is labor intensive, subjective, and can result in some false positive and (many) false negative results. Due to the availability of more sensitive and specific tests (specifically the PCR), it is not recommended for routine diagnosis anymore.
- Polymerase chain reaction (PCR) testing is the preferred method particularly but not exclusively for oral and other lesions where contamination with commensal treponemes is likely. It can be performed using tissues, cerebrospinal fluid (CSF) or blood (although insensitive in the latter). There is no internationally approved PCR assay for *T. pallidum* and accordingly, it is crucial to select a strictly validated and quality-assured method and always use it with appropriate quality controls.
- Immunohistochemistry using a polyclonal antibody against *T. pallidum* can be efficient to identify treponemes in skin, mucosal and tissue lesions, but it is not suitable for routine diagnosis.
- Hybridization in tissues is not used for routine diagnosis.
- Warthin-Starry (argentic) staining on tissues is very difficult to perform and of limited value in most cases.
- (Direct fluorescent antibody test is obsolete)
- For molecular epidemiological typing, PCR, PCR-restriction fragment length polymorphism (RFLP) and/or DNA-sequencing (e.g. multilocus sequence typing (MLST) or whole genome sequencing) can be performed on clinical specimens. However, due to the highly conserved genome of *T. pallidum* the discriminatory ability of typing methods is in general low (Janier et al., 2020)"

Primary Screening Test(s)

- "TT [TPHA, MHA-TP, TPPA or EIA/ELISA/CLIA] – a TT-based screening algorithm, using by preference an automatized EIA/ELISA/CLIA, is used in many large, well-resourced European laboratories and is particularly suitable for automated high-throughput screening of asymptomatic populations including blood/plasma donors. The algorithm identifies persons with previous successful treatment of syphilis as well as those with untreated syphilis. It is usually more sensitive in detecting very early syphilis compared to the use of a screening NTT. However, it can also result in a high number of false positive tests (i.e. very low positive predictive value) in lowprevalence populations.
- NTT [RPR or VDRL] – a NTT-based screening algorithm; preferably quantitative (i.e. to detect prozone phenomenon in infectious syphilis), is still recommended in some countries. In this algorithm, only active (infectious) syphilis is detected, however, it has a lower sensitivity compared to using a TT as primary screening test, and in particular very early syphilis can be missed.
- TT combined with a NTT - this algorithm is particularly useful in cases where the suspicion of very early syphilis is high (recent chancre, contacts of syphilis cases etc.), because in some patients NTT may become reactive before TT (Janier et al., 2020)."

Confirmatory test(s) if any screening test is positive

- "In the case a TT being used alone as a primary screening test, if positive, a confirmatory TT of a different type is of limited value in informing treatment, but a reflex quantitative NTT (reaching at least 1:8 to 1:16 dilution) should be performed in all cases on the same serum (1, B). Although

a confirmatory TT may be important for counselling, notification and may have a psychological impact, it has limited impact on treatment.69 In patients with a positive TT, a negative NTT and no suspicion of very early syphilis (no chancre), both tests should be repeated after 1 month (1, D). However, CLIA and EIA used in many European settings have suboptimal specificity, resulting in a low positive predictive value in low prevalence population. 22,49,56 If such tests are used, additionally a reflex confirmatory test by TPHA or TPPA should be performed (1, C).

- In the case a NTT alone is used as a primary screening test, a positive test must be followed by a reflex TT on the same serum. If quantitative NTT was not initially done, the NTT should be repeated quantitatively (1, B).
- In the case both a TT and a NTT are used as primary screening tests such as (EIA/ELISA/CLIA/TPHA/TPPA plus VDRL/RPR), the NTT must be performed quantitatively (if not initially done) in case of positive or discrepant screening tests (1, B).
- The IgG-immunoblot for Treponema pallidum has no added major value to other TT. It is expensive and interpretation of undetermined immunoblot is elusive (1 to 4 bands).

The Management of Chlamydia Trachomatis Infections **(Lanjouw et al., 2016):** "Appropriate testing of symptomatic and asymptomatic sexually active individual is recommended to identify and treat the *C. trachomatis* infections." With a Grade A recommendation, they recommend using NAATs that identify specific nucleic acid, either DNA or RNA) *of C. trachomatis* "due to their superior sensitivity, specificity, and speed."

The following list contains the indications for laboratory testing as recommended by the IUSTI with a Grade C recommendation (Lanjouw et al., 2016):

Indications for laboratory testing (Level of evidence IV; Grade C recommendation)

- Risk factor(s) for *C. trachomatis* infection and/or other STI (age<25 years, new sexual contact in the last year, more than one partner in the last year);
- Symptoms or signs of urethritis in men;
- Cervical or vaginal discharge with risk factor for STI;
- Acute epididymo-orchitis in a male aged <40 years or with risk factors for STI;
- Acute pelvic pain and/or symptoms or signs of PID;
- Proctitis/proctocolitis according to risk;
- Purulent conjunctivitis in a neonate or adult;
- Atypical neonatal pneumonia;
- Persons diagnosed with other STI;
- Sexual contact of persons with an STI or PID;
- Termination of pregnancy;
- Any intrauterine interventions or manipulations.

The Management of Genital Herpes **(Patel et al., 2017):** The principle change to the IUSTI guidelines in this recent version is that "HSV DNA detection rather than cell culture is now the gold standard for diagnosis." With a grade C recommendation, "serological testing is not routinely recommended in asymptomatic patients." They note that there are specific groups where it may be useful, including pregnant women, sexual partners of HSV-positive people, those with a history of recurrent or atypical

genital disease, and those with first-episode genital herpes whose differentiation may aid in counseling and management (because seroconversion happens typically at 90 days post-infection).

Male Training Center for Family Planning & Reproductive Health (MTC), Office of Population Affairs, Department of Health and Human Services (Marcell & Health, 2014)

In general, the MTC recommends at least annual testing for chlamydia, gonorrhea, syphilis, HIV/AIDS, and Hepatitis C for anyone in an at-risk population, including MSM. For syphilis, certain populations require testing at 3-6 month intervals, including those who exchange sex for drugs, commercial sex workers, and young MSM.

The MTC does not recommend screening for pharyngeal chlamydia infections. They do recommend follow-up test three months after initial positive chlamydia test. They recommend using a urine-based NAAT for chlamydia for at-risk male populations under the age of 25, which include MSM, patients at STI clinics, and military personnel (under the age of 30), and inmates entering jails or detention centers (under the age of 30). Men who have had receptive anal intercourse in the preceding year should have a NAAT performed on a rectal swab to check for rectal chlamydial infection.

The MTC recommends using NAAT for gonorrhea testing of at-risk male adolescents and adults, including MSM. "Males with gonorrhea infection should be re-screened for reinfection at 3 months." Annual exams for MSM include screening for urethral infections, pharyngeal infections using NAAT for those "who have had receptive oral intercourse" during the preceding year, and rectal infections using NAAT of rectal swabs for those "who have had receptive anal intercourse" during the preceding year. "More frequent STD screening (i.e., at 3 – 6 month intervals) is indicated for MSM who have multiple or anonymous partners (Marcell & Health, 2014)."

Canadian Guidelines on Sexually Transmitted Infections (Chernesky, 2018)

"For anal warts, no specific testing is recommended to verify the presence or type of HPV as this will not alter management. Anal Pap and/or HPV testing may be of value to identify precancerous anal intraepithelial neoplasia (AIN) in high-risk groups… Although no products are currently licensed for these [pharyngeal] specimens in Canada, validated NAATs can be used to detect oropharyngeal N. gonorrhoeae and C. trachomatis infections. Confirmation of positives with culture or a second NAAT should be performed." NAAT can be performed on first-void urine samples from male patients or vaginal swabs or urine samples obtained from female patients. Since NAAT allows for the testing of antimicrobial susceptibility in gonorrheal infections, "depending on the clinical situation, consideration should be given to using both culture and NAAT, especially in symptomatic patients." For oral lesions of suspected HSV, they recommend using NAAT or to obtain fluid for culture. "NAATs approach sensitivities and specificities of 100%, with rapid turn-around of results." For syphilis, "NAATs can be used as a non-serological method for identifying *T. pallidum* in mucosa and skin involve. They are very sensitive and specific. When genital lesions characteristic of early syphilis are present, clear serous fluid may be collected for dark-field microscopy, enabling observation of morphology and movement of the spirochetes for the detection of *T. pallidum* (not reliable for oral or rectal lesions)."

American Academy of Pediatrics (AAP) (Murray et al., 2014)

Chlamydia: The AAP recommends annual screening for sexually active females 25 years old or younger. They also recommend annual urethral and rectal chlamydia screenings for sexually active MSM, but more frequent screening (every 3-6 months) for those who are in a higher risk category, such as multiple partners, sex-for-drugs, and so on. Anyone who has been exposed to chlamydia in the past 60 days should also be tested. "Consider screening sexually active males annually in settings with high prevalence rates, such as jails or juvenile corrections facilities, national job training programs, STD clinics, high school clinics, and adolescent clinics for patients who have a history of multiple partners." Anyone who has tested positive for chlamydia should be retested three months after receiving treatment.

Gonorrhea: Similar to chlamydia, the AAP recommends annual screening for sexually active females under the age of 25. "Routinely screen sexually active adolescent and young adults MSM for pharyngeal, rectal, and urethral gonorrhea infection annually if engaging in receptive oral or anal intercourse or insertive intercourse, respectively." Again, like chlamydial infections, those participating in higher risk activities should be tested every 3-6 months. Anyone who has been exposed to gonorrhea in the past 60 days should also be tested. Finally, the screening recommendations for other males are similar to the recommendations concerning chlamydial infections. Anyone who has tested positive for gonorrhea should be retested three months after receiving treatment.

Syphilis: "The routine screening of nonpregnant, heterosexual adolescents is not recommended. However, screening is recommended for all sexually active adolescent and young adults MSM annually or every 3 to 6 months if high risk and can be considered for youth whose behaviors put them at higher risk."

National Institute for Health and Care Excellence (NICE) (NCCC, 2018)

NICE released their guidelines concerning cancer of the upper aerodigestive tract in 2016 (with updates in 2018 online). Recommendation 1.6.1: "Test all squamous cell carcinomas of the oropharynx using p16 immunohistochemistry. Regard the p16 test result as positive only if there is strong nuclear and cytoplasmic staining in more than 70% of tumour cells." In Recommendation 1.6.2: "Consider high-risk HPV DNA or RNA in-situ hybridisation in all p16-positive cancers of the oropharynx to confirm HPV status." In explaining their recommendations, NICE states, "HPV testing is currently recommended in cancer of the oropharynx because it has significant prognostic implication." **National Health Care for the Homeless Council (Audain et al., 2013)**

The National Health Care for the Homeless Council recommends HPV screening along with cervical screening every 6 months for HIV-positive, homeless women. This can be decreased to an annual screening once two consecutive normal Pap smears occur. They also recommend annual gonococcal and chlamydial tests for all HIV-positive patients. "Consider anal Pap smear and tests for rectal *N. gonorrhoeae* and *C. trachomatis* infection at baseline and annually in MSM and any patient with history of anogenital condylomata."

Canadian Paediatric Society (CPS) (Allen, MacDonald, & Canadian Paediatric Society, 2018; Allen, MacDonald, & Top, 2019; Robinson & Canadian Paediatric Society, 2018)

The 2018 update to the CPS practice point titled Congenital syphilis: No longer just of historical interest included the following:

> "Syphilis serology should routinely be performed at the first prenatal visit, followed by appropriate maternal counselling and therapy, if reactive. Rescreening should occur at 28 to 32 weeks' gestation and at delivery in high-risk women, including women who originate from a country with a high prevalence of syphilis. Routine rescreening should also be considered in areas experiencing outbreaks of heterosexual syphilis. If syphilis serology was not performed during pregnancy, newborns should not be discharged from hospital until maternal serology has been drawn and follow-up of results has been arranged. If the cause is not known for a hydropic or stillbirth newborn, the mother should be screened for syphilis postpartum (Robinson & Canadian Paediatric Society, 2018)."

The CPS practice point Sexually transmitted infections in adolescents: Maximizing opportunities for optimal care (Allen et al., 2018) included the following table concerning what screening tests should be used for each condition. These guidelines were updated in 2019, and reaffirmed in 2020 (Allen et al., 2019).

TABLE 1

What screening tests should be used use to detect sexually transmitted infections?

Infection	Screening tests/samples	Follow-up testing
Chlamydia	NAAT is the most sensitive and specific test. Can be performed on urine, urethral swabs, vaginal or cervical swabs* A culture of cervical or urethral specimen is the test of choice for medico-legal cases (eg., sexual assault). Confirmation by NAAT using a different set of primers or DNA sequencing may be used. For pharyngeal and rectal specimens, NAAT may be considered; discuss with testing laboratory	Test-of-cure 3 to 4 weeks after treatment: – Compliance is uncertain – Second-line or alternative treatment was used – Re-exposure risk is high – An adolescent is pregnant
Syphilis	Serology remains the usual diagnostic test unless the patient has lesions compatible with syphilis on the nature of infection, Treponemal-specific screening assays (e.g., EIA) as follows: are more sensitive than non-treponemal tests, Primary, secondary, early though testing algorithms vary across latent infection: Repeat jurisdictions	Follow-up testing depends serology at 1, 3, 6, and 12

	If treponemal-specific assay is positive, a second months after treatment treponemal test is usually required Late latent infection: Repeat serology 12 and 24 months after treatment Neurosyphilis: Repeat 6, 12, and 24 months after treatment	
Gonorrhea	NAAT can be used to detect gonorrhea from urine, and urethral, vaginal and cervical swabs in symptomatic and asymptomatic individuals* Culture allows for antimicrobial susceptibility testing and should be performed if a patient does not promptly respond to therapy Cultures should be submitted for asymptomatic or symptomatic MSM, who have an increased incidence of antibiotic resistance For rectal and pharyngeal testing, discuss preferred specimens with the testing laboratory Culture is preferred for pharyngeal and rectal specimens For medico-legal purposes, a positive result obtained from NAATs should be confirmed using culture or a different set of primers, or by DNA sequencing techniques	Test-of-cure (culture 3 to 7 days post-treatment or NAAT 2 to 3 weeks later) if: – Second-line or alternative treatment was used – Antimicrobial resistance is a concern – Compliance is uncertain – Re-exposure risk is high – An adolescent is pregnant – Previous treatment failure – Pharyngeal or rectal infection – Infection is disseminated – Signs, symptoms persist post-treatment

**Discuss specimen selection to ensure that the NAAT is validated for the specimen to be collected and the patient being tested. For example, NAAT testing has not been validated for children ≤12 years of age and for medico-legal specimens.*

British Association for Sexual Health and HIV (BASHH) (Bignell & Fitzgerald, 2011; Kingston et al., 2016; Nwokolo et al., 2016; Patel et al., 2015; White, O'Farrell, & Daniels, 2013)

UK National Guideline for the Management of Lymphogranuloma Venereum (White et al., 2013):
"Commercial molecular diagnostic techniques to detect *C. trachomatis* remain the primary test of choice, with referral of *C. trachomatis*-positive specimens for molecular tests to confirm the presence of LGV-associated DNA." Testing should be performed on anyone exhibiting symptoms of an LGV infection, including hemorrhagic proctitis, primary lesions, suspected LGV-associated pharyngitis, secondary lesions, buboes, lymphadenitis, and/or lymphadenopathy. Main diagnostic techniques include using either NAATs, "culture on cycloheximide-treated McCoy cells of material from suspected LGV lesions," or serology testing.f "Serology cannot necessarily distinguish past from current LGV infection, which might prove restrictive given the high number of recurrent LGV infections now seen in MSM."

UK National Guideline for the Management of Anogenital Herpes (Patel et al., 2015): The clinical signs and symptoms of an HSV infection can include "painful ulceration, dysuria, vaginal or urethral discharge" as well as systemic symptoms of fever and myalgia. Other signs can include bilateral lymphadenitis—although, alternating sides can occur in subsequent episodes—and proctitis. With a Grade C recommendation, "The confirmation and typing of the infection and its type, by direct detection of HSV in genital lesions, are essential for diagnosis, prognosis, counselling, and management." BASHH gives an "A" recommendation of directly testing swabs from either anogenital lesions or the rectal mucosa in suspected proctitis. They recommend with a "B" rating that virus typing be performed to differentiate HSV-1 from HSV-2 in newly diagnosed cases of genital herpes. NAATs are the preferred testing method (grade "A" recommendation) since HSV culture tests can miss around 30% of PCR-positive samples.

UK National Guideline for the Management of Infection with Chlamydia Trachomatis (updated 2018) (Nwokolo et al., 2016): "Testing for genital and extra-genital chlamydia should be performed using NAATs (Grade B)." MSM who test positive for both HIV and chlamydia should be tested for LGV even if asymptomatic for the latter (Grade B). They give a Grade B recommendation for LGV testing in patients presenting with proctitis and a Grade C recommendation for treating both sexes presenting with proctitis the same.

The guidelines were updated in 2018, but NAAT testing is still considered the current standard of care for all chlamydia cases by the BASHH; "Although no test is 100% sensitive or specific, NAATs are known to be more sensitive and specific than EIAs" (BASHH, 2018).

UK National Guidelines on the Management of Syphilis (updated 2017, 2019) (Kingston et al., 2016): They recommend (2A) "where appropriate expertise and equipment are available, perform dark ground microscopy on possible chancres" and (1A) that "*T. pallidum* testing by PCR is appropriate on lesions where the organism may be expected to be located." Within the section on serology, they recommend (1B) that "An EIA/CLIA, preferably detecting both IgM and IgG IS the screening test of choice"; "positive screening tests should be confirmed with a different treponemal test (not the FTAabs) and a second specimen for confirmatory testing obtained" (1B); "a quantitative RPR or VDRL should be performed when screening tests are positive" (1A); and (1B) repeat testing for syphilis at 6 and 12 weeks if an isolated episode and "at two weeks after possible chancres that are dark-ground and/or PCR negative are observed." These guidelines were updated in 2017 and 2019, but diagnostic testing methods were not changed.

Cumulative Guideline Table			
Year & Society	**Condition**	**Microorganism**	**Recommendation**
2020 NCCN	Anal Carcinoma	HPV	HPV linked to anal cancers and HPV positivity linked to positive OS

Cumulative Guideline Table			
Year & Society	**Condition**	**Microorganism**	**Recommendation**
2020 NCCN	Cervical Cancer	HPV	Overwhelming evidence of link between HPV and cervical cancer; chronic HPV infection status used in aiding treatment/surgical options
2020 NCCN	Head and Neck Cancers/ Oropharyngeal Cancer	HPV	Requires HPV p16 testing by IHC; HPV status is imperative in determining therapy
2020 NCCN	Occult Primary Cancers (Squamous Cell Carcinoma)	HPV	If clinical presentation in the head and neck nodes is noted, check p16 IHC and ISH results
2020 NCCN	Penile Cancer	HPV	HPV linked to penile cancer; HPV status of lesions important for determining therapy
2020 NCCN	Vulvar Cancer (Squamous Cell Carcinoma)	HPV	HPV linked to vulvar cancer, especially HSIL; recommends HPV testing for "appropriate patients"
2014 USPSTF	NA	Chlamydia, Gonorrhea	Testing in sexually active women age 24 or younger and older women of at-risk populations; insufficient evidence concerning routinely screening in general population of males
2014 USPSTF	Oropharyngeal Cancer	HPV	Insufficient evidence to assess testing for HPV in cases of asymptomatic oropharyngeal cancer

2016 USPSTF	Asymptomatic Genital Herpes	HSV-2	Do not recommend testing asymptomatic patients for HSV-2

Cumulative Guideline Table			
Year & Society	**Condition**	**Microorganism**	**Recommendation**
2016 USPSTF	NA	Syphilis	Grade A recommendation for screening asymptomatic patients of HIGH RISK categories but they do NOT recommend screening in asymptomatic patients not in high risk categories; recommend screening HIVpositive men and MSM every three months
2015 CDC	Genital, Anal, or Perianal Ulcers	Syphilis, HSV	Recommends syphilis serology, darkfield exam, or PCR testing if possible; culture or PCR for genital herpes; serologic testing for type-specific HSV antibody
2015 CDC	NA	Syphilis	Darkfield examination of exudate can be used for early diagnosis; presumptive diagnosis requires use of two tests—both a treponemal test and a nontreponemal test; any signs of CNS infection require additional testing
2015 CDC	NA	Chlamydia	Testing of women under age of 25 as well as older women and men if they fall in a high-risk category; do NOT recommend testing of asymptomatic men and older women

2015 CDC	NA	Gonorrhea	Testing of women under age of 25 as well as older women and men if they fall in a high-risk category; do NOT recommend testing of asymptomatic men and older women; men showing

Cumulative Guideline Table			
Year & Society	**Condition**	**Microorganism**	**Recommendation**
			signs of urethral gonococcal infection should be tested
2015, 2016 CDC	NA	HPV	Recommends against using oncogenic HPV testing for asymptomatic men, women aged 25 and over, or for general STD testing. There is no approved test for HPV in men, and routine testing is not recommended for anal, penile, or throat cancers in men.
2015 CDC	Anogenital Warts	HPV	"HPV testing is not recommended for anogenital wart diagnosis, because test results are not confirmatory and do not guide genital wart management."

2015, 2019 CDC	Cervical Screening	HPV	For women aged 30 or older, HPV testing can be part of cervical screening. For women ages 30-65, if co-testing Pap test and HRHPV, then frequency is every 5 years…if only doing a Pap test, the frequency is every 3 years HPV tests to screen for cervical cancer are recommended for women 30 years and older. They are not recommended to screen, men, adolescents, or women under the age of 30.
2019 IUSTI	Anogenital Warts	HPV	Do not recommend HPV testing for symptomatic anogenital warts since it

Cumulative Guideline Table			
Year & Society	**Condition**	**Microorganism**	**Recommendation**
			adds no information for clinical use.
2012 IUSTI (published in 2013)	NA	Gonorrhea	Culture testing is only method to determine antimicrobial susceptibility, but NAAT testing is more sensitive. Includes list of symptoms for testing.

2019 IUSTI	Lymphogranuloma venereum	Chlamydia	To diagnose LGV, a sample tested *C. trachomatis* positive with a commercial nucleic acid amplification test (NAAT) platform should be confirmed with an LGV discriminatory NAAT. For sensitive and specific LGV detection, laboratories are recommended to use a twostep procedure.
2014, 2020 IUSTI	NA	Syphilis	Like the CDC, they recommend a two-test method for diagnosing syphilis (one nontreponema test and one treponema test) if any initial screening test is positive
2015 IUSTI (published in 2016)	NA	Chlamydia	Recommends using an NAAT for chlamydia testing and lists signs/symptoms that require testing
2017 IUSTI	Genital herpes	HSV	Typically, does not recommend testing in asymptomatic patients; HSV DNA detection now replaces culture as gold standard
2014 MTC	NA	Chlamydia	Do not recommend pharyngeal screenings. Do recommend NAAT of at-risk groups with a 3-month

Cumulative Guideline Table			
Year & Society	**Condition**	**Microorganism**	**Recommendation**
			follow-up test for patients who tested positive

2014 MTC	NA	Gonorrhea	Do recommend annual NAAT of at-risk groups with a 3-month follow-up test for patients who tested positive; more frequent testing in certain MSM populations
2014 MTC	NA	Syphilis	Do recommend annual testing of at-risk groups with 3-6 month testing of certain populations (commercial sex workers, inmates of correctional facilities, persons who exchange sex for drugs, and so on)
2018 Canadian Guidelines on STIs	NA	Chlamydia, Syphilis, Gonorrhea, HSV, and HPV	NAATs are more specific and sensitive than culture testing when available. For gonorrheal infections, only culture can test for antimicrobial susceptibility in gonorrhea.
2014 AAP	Adolescents & young adults	Chlamydia, Gonorrhea	All sexually active young women (under the age of 25) and MSM should have annual screenings. For those at higher risk, they should be screened every 3-6 months. Anyone who tests positive should be retested 3 months after receiving treatment.
2014 AAP	Adolescents & young adults	Syphilis	Do NOT recommend routine screening except for sexually active young MSM.

Cumulative Guideline Table			
Year & Society	**Condition**	**Microorganism**	**Recommendation**

2016 NICE	Oropharyngeal Cancers	HPV	Test all carcinomas of the oropharynx using p16 IHC; consider using high-risk HPV DNA/RNA in situ hybridization in all p16positive cancers
2013 National Health Care for the Homeless Council	HIV/AIDS	HPV	For women, every 6 months along with Pap for HIVpositive patients; decrease to annual after two consecutive normal Pap tests
2013 National Health Care for the Homeless Council	HIV/AIDS	Chlamydia, Gonorrhea	Annual testing of all HIVpositive patients; consider anal Pap smear and rectal tests for MSM annually
2013 National Health Care for the Homeless Council	HIV/AIDS with anogenital condylomata	Chlamydia, Gonorrhea	Consider annual anal Pap smear and rectal tests for both chlamydia and GC for patients with history of anogenital condylomata
2018 CPS	Pregnant women	Syphilis	Testing at first prenatal visit as well as 28-32 weeks; if not tested during pregnancy, child does not leave the hospital without being tested
2020 CPS	Adolescents/young adults	Chlamydia, Syphilis, Gonorrhea	See detailed testing and frequency in table within the guidelines above
2015 BASHH (published in 2016)	NA	Syphilis	Dark-field microscopy or PCR tests can be performed. For serology, EIA/CLIA is the screening test of choice (preferably where both IgM
Cumulative Guideline Table			

Year & Society	Condition	Microorganism	Recommendation
			and IgG are detected). Positive tests must be followed by a quantitative RPR or VDRL.
2013 BASHH	Suspected LGV	Chlamydia	Testing should use either NAAT, culture testing, or serology; however, the latter cannot distinguish current from past infections.
2014 BASHH (published in 2015)	Anogenital herpes	HSV	NAAT is preferred over other forms of testing ("A" grade). Differentiation of virus type should be determined on new cases of genital herpes ("B" grade).
2015, 2018 BASHH	NA	Chlamydia	Test for chlamydia using NAATs. Both sexes presenting with proctitis should be treated the same with respect to LGV testing. HIV-positive men with chlamydia should also be tested for LGV, even if asymptomatic.
Abbreviations: CLIA = chemiluminescent assay; EIA = enzyme immunoassay; GC = gonococcal; HPV = human papillomavirus; HR-HPV = high risk or oncogenic HPV testing; HSIL = high-grade squamous intraepithelial lesions; HSV = herpes simplex virus; IHC = immunohistochemistry; LGV = lymphogranuloma venereum; MSM = men having sex with men; NA = not applicable; NAAT = nucleic acid amplification testing; OS = overall survival; RPR = rapid plasma reagin test; VDRL = Venereal Diseases Research Laboratory carbon antigen test			

VI. State and Federal Regulations, as applicable

The FDA approved the BD Onclarity HPV Assay, a qualitative in vitro assay of cervical swabs using PCR (i.e. a nucleic acid amplification test or NAAT), by Becton, Dickinson and Company on 02/12/2018. "The test specifically identifies types 16, 18 and 45 while concurrently detecting the other HR HPV types that include 31, 33, 35, 39, 51, 52, 56, 58, 59, 66 and 68. The BD Onclarity HPV Assay is indicated: 1) In women 21 years and older with ASC-US (atypical squamous cells of undetermined significance) cervical cytology test results, the BD Onclarity HPV Assay can be used to determine the need for

referral to colposcopy;2) In women 21 years and older with ASC-US cervical cytology test results, the BD Onclarity HPV assay can be used to detect high-risk HPV genotypes 16, 18 and 45. This information together with physicians assessment of screening history, other risk factors, and professional guidelines, may be used to guide patient management. The results of this test are not intended to prevent women from proceeding to colposcopy;3) In women 30 years and older, the BD Onclarity HPV Assay can be used together with cervical cytology to adjunctively screen to detect high risk HPV types. This information, together with the physicians assessment of screening history, other factors, and professional guidelines, may be used to guide patient management;4) In women 30 years and older, the BD Onclarity HPV Assay can be used to detect high-risk HPV genotypes 16, 18 and 45. This information, together with the physicians assessment of screening history, other factors, and professional guidelines, may be used to guide patient management; and5) In women 25 years and older, the BD Onclarity HPV Assay can be used as a first-line primary cervical cancer screening test to detect high risk HPV, including 16 and 18. Women who test negative for the high risk HPV types by the BD Onclarity HPV Assay should be followed up in accordance with the physicians assessment of screening and medical history, other risk factors, and professional guidelines. Women who test positive for HPV genotypes 16 and/or 18 by the BD Onclarity HPV Assay should be referred to colposcopy. Women who test high risk HPV positive and 16 and 18 negative by the BD Onclarity HPV Assay (12 other HR HPV Positive) should be evaluated by cervical cytology to determine the need for referral to colposcopy (FDA, 2018a)." Further, BD recently reported that the BD Onclarity Assay received FDA approval for extended genotyping capabilities beyond HPV genotypes 16, 18, and 45; genotypes 31, 51, 52, 33/58, 35/39/68, and 56/59/66 are now included. This is "the only FDAapproved assay to individually identify and report these genotype results" (BD, 2020).

The FDA has also approved the APTIMA HPV 16 18/45 Genotype Assay, a NAAT, for the qualitative detection of mRNA for HPV 16, 18, and 45 from Gen-Probe Incorporated on 10/12/2012; however, this test cannot distinguish between 18 and 45. Previously, on 10/28/2012, the FDA approved GenProbe Incorporated's APTIMA HPV Assay, an NAAT that tests for 14 high-risk types of HPV but is unable to distinguish between the 14 types. The COBAS HPV test by Roche Molecular Systems, Inc. was approved by the FDA on 04/19/2011 as a NAAT for 14 high-risk types of HPV. This test can specifically identify HPV 16 and 18 but cannot distinguish from the other 12 types of HPV. Hologic, Inc. has two FDA-approved HPV NAAT tests—Cervista HPV 16/18 and Cervista HPV HR and GENFIND DNA Extraction Kit. Both were approved on 03/12/2009. The former is a fluorescent, isothermal-based reaction that detects HPV 16 and 18 whereas the latter screens for DNA from the 14 high-risk HPV strains (FDA, 2018b).

The FDA has approved many tests for HSV, chlamydia, gonorrhea, and syphilis. A search of the FDA Devices database of "HSV" on 09/24/2020 yielded 108 results. Likewise, a search of "chlamydia" and "syphilis" had 143 and 36 records, respectively. "Neisseria" and "gonorrhea" yielded a combined 59 records of approved FDA devices as of 09/24/2020. "Trichomonas" yielded 17 records of approved FDA devices as of 09/24/2020 (FDA, 2020).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
86592	Syphilis test, non-treponemal antibody; qualitative (eg, VDRL, RPR, ART)
86593	Syphilis test, non-treponemal antibody; quantitative
86631	Antibody; Chlamydia
86632	Antibody; Chlamydia, IgM
86694	Antibody; herpes simplex, non-specific type test
86695	Antibody; herpes simplex, type 1
86696	Antibody; herpes simplex, type 2
86780	Antibody; Treponema pallidum
87081	Culture, presumptive, pathogenic organisms, screening only;
87110	Culture, chlamydia, any source
87181	Susceptibility studies, antimicrobial agent; agar dilution method, per agent (eg, antibiotic gradient strip)
87490	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, direct probe technique
87491	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, amplified probe technique
87492	Infectious agent detection by nucleic acid (DNA or RNA); Chlamydia trachomatis, quantification
87528	Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, direct probe technique
87529	Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, amplified probe technique
87530	Infectious agent detection by nucleic acid (DNA or RNA); Herpes simplex virus, quantification
87590	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, direct probe technique

87591	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, amplified probe technique
87592	Infectious agent detection by nucleic acid (DNA or RNA); Neisseria gonorrhoeae, quantification

87623	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), low-risk types (eg, 6, 11, 42, 43, 44)
87624	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), high-risk types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
87625	Infectious agent detection by nucleic acid (DNA or RNA); Human Papillomavirus (HPV), types 16 and 18 only, includes type 45, if performed
87660	Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, direct probe technique
87661	Infectious agent detection by nucleic acid (DNA or RNA); Trichomonas vaginalis, amplified probe technique
87797	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; direct probe technique, each organism
87798	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism
87799	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; quantification, each organism
87808	Infectious agent antigen detection by immunoassay with direct optical observation; Trichomonas vaginalis
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure

88344	Immunohistochemistry or immunocytochemistry, per specimen; each multiplex antibody stain procedure
0064U	Antibody, Treponema pallidum, total and rapid plasma reagin (RPR), immunoassay, qualitative Proprietary test: BioPlex 2200 Syphilis Total & RPR Assay Lab/Manufacturer: Bio-Rad Laboratories
0065U	Syphilis test, non-treponemal antibody, immunoassay, qualitative (RPR)
	Proprietary test: BioPlex 2200 RPR Assay Lab/Manufacturer: Bio-Rad Laboratories
0096U	Human papillomavirus (HPV), high-risk types (ie, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68), male urine Proprietary test: HPV, High-Risk, Male Urine Lab/Manufacturer: Molecular Testing Labs/Roche Cobas
0210U	Syphilis test, non-treponemal antibody, immunoassay, quantitative (RPR) Proprietary test: BioPlex 2200 RPR Assay - Quantitative Lab/Manufacturer: Bio-Rad Laboratories
0500T	Infectious agent detection by nucleic acid (DNA or RNA), Human Papillomavirus (HPV) for five or more separately reported high-risk HPV types (eg, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) (ie, genotyping)

VIII. Evidence-based Scientific References

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IX. Revision History

Revision Date	Summary of Changes
06-01-2021	Initial presentation