SYPHILIS TESTING

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INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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BACKGROUND

*Treponema pallidum*, a bacterium with a corkscrew appearance and spiraling motility, causes syphilis, a multisystem disease with a potentially lengthy and destructive clinical course. Though classified as a sexually transmitted disease, the infection can also be spread by transfusion and vertically during pregnancy or delivery. In the United States, the incidence peaked during World War II but spiked again in the mid-2000s in the population of men who have sex with men. In 2010, 67% of cases occurred in this high-risk group. From 2009-2010, there were 8.7 cases of congenital syphilis per 100,000 live births in the United States.

Because the general population is not screened for infection, healthcare providers must be able to identify risk factors and signs of syphilis in order to test for the disease as warranted. The organism cannot be cultivated *in vitro*; therefore, indirect methods are used to establish infection. Serologic assays, including the venereal
disease reference laboratory (VDRL), the rapid plasma reagin (RPR), and treponemal tests, are the mainstay of laboratory diagnosis. The organism has remained sensitive to penicillin therapy, even after decades.

Syphilis is a systemic disease with a waxing and waning course characterized by several discrete disease phases. The incubation phase ranges from 10 to 90 days. In cases that are sexually transmitted, the primary phase is marked by a painless solitary ulcer at the site of inoculation and regional lymphadenopathy can also ensue. The primary chancre lasts 4-6 weeks, and signs of the secondary phase usually occur within 3 months of the primary infection. Syphilis d’embrée is syphilis without a chancre and is characteristic of congenital syphilis and syphilis acquired by transfusion. In congenital cases, the early phase is heralded by rhinitis followed by a rash that can become desquamative. In transfusion-acquired cases, infection can present with the rash characteristic of secondary syphilis.\(^2\)

A maculopapular rash, generalized lymphadenopathy, and nonspecific systemic symptoms such as malaise characterize secondary syphilis. Less commonly, secondary syphilis can also affect the stomach, liver, and kidney. Syphilitic hepatitis is often associated with syphilitic proctitis, for which anal intercourse is a risk factor. Most of the systemic problems caused by the organism are due to obliterative endarteritis.

In 40% of untreated patients, the disease can progress to tertiary syphilis after latent periods of 3 to 10 years. Gummata, granulomatous-like lesions, can develop in skin, soft tissue, and bone in 15% of these cases. Cardiovascular manifestations include aortic insufficiency or aortic aneurysm. Neurologic involvement may be present. It has been suggested that an RPR titer greater than or equal to 1:32 is associated with neurosyphilis.\(^2\) Acute neurosyphilis is characterized by symptoms similar to those experienced with meningitis (headache, nausea and vomiting, and nuchal rigidity). Chronic neurosyphilis may have an asymptomatic or symptomatic course. The asymptomatic variety is more common and is defined by the presence of one or more CSF (cerebrospinal fluid) abnormalities in the absence of clinical manifestations of neurosyphilis. These abnormalities can include CSF findings that are characteristic of a bacterial meningitis (increased protein concentration, decreased glucose concentration, and pleocytosis) and/or a positive nontreponemal CSF test. The symptomatic course can present as meningovascular neurosyphilis or as parenchymatous neurosyphilis. Although the findings of neurosyphilis are not specific, some of the characteristic signs include the Argyll Robertson pupil that accommodates to near vision but not light, constriction of the visual field, deafness due to damage to the auditory nerve, and loss of facial expression due to facial nerve involvement.

Congenital syphilis is asymptomatic in two-thirds of live-born cases. When the disease is spread vertically, fetal demise results in 40% of cases due to second trimester spontaneous abortion or late-term stillbirth. Additionally, the disease can cause premature birth. Manifestations of congenital syphilis are categorized as early or late, with late signs occurring after the first two years of life. The earliest sign is rhinitis followed by a rash that can become desquamous. Bone disease is the most common sign of early syphilis.\(^3\) The liver is frequently affected; therefore, anemia, splenomegaly, and jaundice may be present. Other organs severely affected include the brain, lung, and skeletal system. Glomerulonephritis can also occur. Late signs include Hutchinson’s teeth, saddle nose, and saber shins. Untreated early perinatal syphilis is fatal in up to 40% of cases.\(^1\) Fatality inversely correlates with the number of prenatal visits.\(^4\)

While HIV-2 does not alter the course of syphilis, HIV-1 does. Persons with HIV-1 infection acquire syphilis more readily, tend to have a worse course of illness with a higher likelihood of treatment failure, and have nonstandard serologic responses. A person coinfected with HIV and syphilis has a greater likelihood of transmitting HIV, which further justifies the need to develop a vaccine for syphilis. HIV patients are more likely to develop neurosyphilis. As many as 11% of HIV patients have a false-positive result with serologic tests for
syphilis.\textsuperscript{5} Patients with HIV commonly have a persistent high titer of RPR or VDRL, especially in early, untreated HIV.

**Testing for Syphilis**

Serologic tests are currently the primary means for making a clinical diagnosis of syphilis. The main types of serologic tests are nontreponemal tests, which reflect the host immune response to cellular damage caused by the pathogen, and more specific (treponemal) tests that measure antibodies against \textit{T. pallidum} antigens.

The nontreponemal tests detect antibodies produced in response to syphilis using antigens found in host cells. The assays commonly employed are the VDRL and the RPR. Since these tests are inexpensive and rapid, they are highly useful for both initial screening and monitoring of treatment. These tests become positive 1-4 weeks after the chancre appears. Patients have their highest reactivity during secondary and early latent syphilis. The nontreponemal tests have a sensitivity of 78-86\% for detecting primary syphilis, 100\% sensitivity for detecting secondary syphilis, and 95-98\% sensitivity for detecting latent syphilis. The specificity is 85-99\%.\textsuperscript{6} When screening patients, false-positive results are possible in the setting of other infections, intravenous drug use, pregnancy, malignancy, advanced age, and autoimmune disease. False positives occur in 1-2\% of the US population.\textsuperscript{7} At least 25\% of people become VDRL- or RPR-negative over time without treatment.

Quantitative nontreponemal tests are used to monitor therapy. For treated patients, it is expected that the VDRL should become nonreactive one year following treatment for primary syphilis and two years after treatment for secondary syphilis. Patients treated with late syphilis may not become nonreactive until the fifth year following therapy. If a patient remains persistently reactive after therapy, it must be determined clinically if this finding represents a false-positive reaction, a persistent active infection, reinfection (especially if the titer is higher than 1:4), or HIV infection.

The treponemal tests are used to verify a nontreponemal reaginic test result. The FTA-ABS (fluorescent treponemal antibody-absorbed assay) is the standard test used and is considered the most sensitive assay to confirm early infection. The test measures antibodies to \textit{T. pallidum} antigens. Other specific tests include particle agglutination tests (\textit{T. pallidum} particle agglutination, \textit{T. pallidum} hemagglutination assay, and microhemagglutination assay for \textit{T. pallidum}) and Western immunoblotting, which is often used to diagnose congenital syphilis. Treponemal tests cannot distinguish active disease from inactive disease because they stay positive in greater than 90\% of adequately treated patients. These tests are more specific and expensive than the nontreponemal tests, although false positives can occur with collagen vascular disease, autoimmune hemolytic anemia, alcoholic cirrhosis, and pregnancy. Infections with other spirochetes, \textit{Leptospira} and \textit{Borrelia burgdorferi}, are less common causes of false-positive FTA-ABS reactions.

Some laboratories perform the treponemal test first and confirm with nontreponemal tests. The cost-effectiveness of this new reversal of testing order has not been established. One analysis of this algorithm performed by the Centers for Disease Control and Prevention (CDC) found that it would cost more for an additional case treated using this practice.\textsuperscript{8} It has been suggested that this algorithm could result in overdiagnosis and overtreatment of syphilis.\textsuperscript{7} The CDC still recommends that the nontreponemal test be used before the treponemal test, but when laboratories reverse this sequence, the CDC recommends using a second treponemal test in cases where the initial treponemal test is positive but the follow-up nontreponemal test is negative.\textsuperscript{9}
Newer enzyme immunoassays have been developed that include treponemal and nontreponemal formats. Currently no rapid tests are cleared by the Food and Drug Administration, although many rapid tests are commercially available. These tests require confirmation with quantitative nontreponemal tests to discriminate active syphilis from treated syphilis and to monitor therapy. Efforts to find an assay that would improve sensitivity in early syphilis have included the use of recombinant *T. pallidum* antigens.

A diagnosis of neurosyphilis requires examination of the spinal fluid. A false-positive CSF VDRL is extremely rare; therefore, a positive CSF VDRL is diagnostic of neurosyphilis. Nonetheless, a CSF sample contaminated with peripheral blood will cause the CSF VDRL result to be positive. Use of CSF FTA-ABS is discouraged because it may cause overdiagnosis of neurosyphilis. The VDRL is the only approved test to detect syphilis in CSF. It is important to note that the CSF VDRL, unlike the peripheral blood VDRL, is not an indicator of disease activity. The CSF VDRL may remain reactive after successful treatment. Thus, other indicators such as CSF cell count and protein concentration are a better reference of disease activity.

The diagnosis of congenital syphilis in a newborn is problematic given that maternal IgG antibodies cross the placenta. Passively transferred antibodies are not detected after 3 months. The maternal serologic status for syphilis should be determined if syphilis is suspected in a newborn. Cord blood should not be tested to establish a diagnosis of congenital syphilis because of the likelihood of false-positive and false-negative results. When fetal nontreponemal assays are interpreted, a rising titer over the period of 6 months is diagnostic of congenital syphilis. Infant serum should not be subjected to treponemal testing since positive tests may be from maternal antibody and negative tests do not rule out infection. The FDA has approved an IgM enzyme immunoassay for the diagnosis of congenital syphilis. A diagnosis of congenital syphilis is confirmed or definite when the organism is identified by darkfield exam, direct fluorescent antibody, or special stains from clinical specimens including biopsies, amniotic fluid, the placenta, the umbilical cord, or autopsy sections. Radiographs can also be helpful to identify skeletal signs such as osteochondritis.

**Society Guidelines**

The United States Preventive Services Task Force (USPSTF) recommends that clinicians should screen all persons at increased risk for syphilis, including men who have sex with men, commercial sex workers, those persons who exchange sex for drugs, and people in adult correctional facilities. The task force has not determined an optimal rescreening interval. The USPSTF does not recommend screening for syphilis in individuals diagnosed with other sexually transmitted diseases. The task force does recommend testing all pregnant women at their first prenatal visit with additional testing later for women in high-risk groups including substance abuse, poverty, African-American ethnicity, and limited access to health care and regular prenatal care.

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists recommend serologic testing for syphilis at the first prenatal visit, after exposure to an infected partner, and at the time of delivery, with additional testing of high-risk women at the beginning of the third trimester. The CDC and the American Academy of Family Physicians recommend testing of all pregnant women for syphilis with repeat testing at 28 weeks and at the time of delivery if indicated.

The CDC recommends testing for syphilis in victims of sexual assault with repeat testing at 6 weeks, 3 months, and 6 months if the initial test is negative. The CDC recommends infants born to mothers with reactive nontreponemal and treponemal tests should have a quantitative nontreponemal test performed on infant serum. The CDC recommends syphilis testing for any woman who delivers a stillborn infant after 20 weeks gestation. The CDC recommends all persons who have syphilis should be tested for HIV.
POLICY

For the following CPT code(s) in Table 1, the patient should have a diagnosis (ICD-10-CM) code(s) listed in the attached files below.

Table 1. HCPCS Codes (Alphanumeric, CPT® AMA)

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<td>86592</td>
<td>Syphilis test, non-treponemal antibody; qualitative (e.g., VDRL, RPR, ART)</td>
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<tr>
<td>86593</td>
<td>Syphilis test, non-treponemal antibody; quantitative</td>
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<tr>
<td>86780</td>
<td>Antibody; Treponema pallidum</td>
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ICD-10 Diagnosis Codes (Proven)

CMP-042 Syphilis
ICD10_v2.3
REFERENCES


<table>
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<tr>
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<th>Action/Description</th>
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<tr>
<td>12/07/2017</td>
<td>Annual Policy Review Completed. Updated ICD10 codes as per CMS recommendations.</td>
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<tr>
<td>01/21/2017</td>
<td>Updated ICD10 codes as per CMS recommendations. Removed ICD9 code file.</td>
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<tr>
<td>12/03/2015</td>
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<tr>
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<td></td>
<td>Added ICD10 diagnosis codes related to high sexual risk:</td>
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<tr>
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<td>Z01.411, Z01.419, Z86.19</td>
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<tr>
<td>10/01/2015</td>
<td>Removed ICD9 table. Embedded ICD9/ ICD10 PDF files.</td>
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