Novel *Treponema pallidum* Serologic Tests: A Paradigm Shift in Syphilis Screening for the 21st Century

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The mainstay of diagnosis for *Treponema pallidum* infections is based on nontreponemal and treponemal serologic tests. Many new diagnostic methods for syphilis have been developed, using specific treponemal antigens and novel formats, including rapid point-of-care tests, enzyme immunoassays, and chemiluminescence assays. Although most of these newer tests are not yet cleared for use in the United States by the Food and Drug Administration, their performance and ease of automation have promoted their application for syphilis screening. Both sensitive and specific, new screening tests detect antitreponemal IgM and IgG antibodies by use of wild-type or recombinant *T. pallidum* antigens. However, these tests cannot distinguish between recent and remote or treated versus untreated infections. In addition, the screening tests require confirmation with nontreponemal tests. This use of treponemal tests for screening and nontreponemal serologic tests as confirmatory tests is a reversal of long-held practice. Clinicians need to understand the science behind these tests to use them properly in syphilis management.

Syphilis, once known as the Great Pox, continues to challenge clinicians with its nuances in diagnosis and management [1]. On the basis of the Wasserman test introduced >100 years ago [2], syphilis diagnosis continues to rely on serologic assays because *Treponema pallidum* cannot be cultured in vitro. Furthermore, direct visualization of the spirochete requires lesions and either fluorescent antibodies or a dark-field microscope, neither of which may be readily available. *T. pallidum* nucleic acid amplification tests are not widely available for use by clinical laboratories. Thus, serologic tests are the foundation of syphilis management, and knowledge of their diagnostic limitations is critical for clinicians.

Several syphilis serologic tests have been cleared for use in the United States by the Food and Drug Administration (FDA) as diagnostic, confirmatory, and blood donor screening tests. However, more syphilis tests are commercially available, primarily because of less stringent procedures for their development internationally [3]. In contrast to older methods, such as the rapid plasma reagin (RPR) test, that use phospholipid (nontreponemal) antigens, newer serologic tests use specific *T. pallidum* antigens. These new technologies have flooded international markets because of their automation. Although most are not cleared by the FDA, these assays may be used after validating their performance in comparison with reference standards. The new treponemal-specific assays have displaced nontreponemal tests for screening in some laboratories and have the potential to confuse clinical management. This review focuses on new serologic tests that have been most widely evaluated for screening of noncongenital syphilis.

**T. pallidum and Antibody Responses**

*Classification and structure.* *T. pallidum* is a fastidious, microaerophilic spirochete that has 4 subspecies (subspecies *pallidum* [venereal syphilis], subspecies *en-...
Table 1. Sensitivity and Specificity of Serologic Tests for Syphilis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity during stage of infection, % (range)</th>
<th>Specificity, % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary</td>
<td>Secondary</td>
</tr>
<tr>
<td>Nontreponemal tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDRL [14]</td>
<td>78 (74–87)</td>
<td>100</td>
</tr>
<tr>
<td>TRUST [14]</td>
<td>85 (77–86)</td>
<td>100</td>
</tr>
<tr>
<td>RPR [14]</td>
<td>86 (77–99)</td>
<td>100</td>
</tr>
<tr>
<td>Early treponemal tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHA-TP [15]</td>
<td>76 (69–90)</td>
<td>100</td>
</tr>
<tr>
<td>TPPA [16]</td>
<td>88 (86–100)</td>
<td>100</td>
</tr>
<tr>
<td>TPHA [17]</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>FTA-ABS [14]</td>
<td>84 (70–100)</td>
<td>100</td>
</tr>
<tr>
<td>Enzyme immunoassays</td>
<td></td>
<td></td>
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<tr>
<td>IgG-ELISA [18]</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>IgM-EIA [19]</td>
<td>93</td>
<td>85</td>
</tr>
<tr>
<td>ICE [20]</td>
<td>77</td>
<td>100</td>
</tr>
<tr>
<td>Immunochemiluminescence assays</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLIA [21]</td>
<td>98</td>
<td>100</td>
</tr>
</tbody>
</table>

NOTE. CLIA, chemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption assay; ICE, immune-capture EIA; MHA-TP, microhemagglutination assay for Treponema pallidum; NA, not available; TPHA, T. pallidum hemagglutination assay; TPPA, Treponema pallidum particle agglutination; TRUST, toluidine red unheated serum test.

Serologic Syphilis Tests

Nontreponemal tests. Three nontreponemal tests are available in the United States that use antigens containing cardiolipin, lecithins, and cholesterol, which flocculate on reaction with IgM and IgG antibodies [13]: the RPR test, the Venereal Disease Research Laboratory (VDRL) test, and the toluidine red unheated serum test (Table 1). Their basis is still imperfectly understood because the antigens are normal components of host cells in humans. Apparently, T. pallidum infection results in binding of host lipids to the treponeme, converting inert lipids into immunogens in vivo [22]. Seroconversion typically occurs...
within 21 days of exposure but may occur up to 6 weeks after infection [23]. Advantages to these tests are that they are inexpensive and simple to perform. Furthermore, quantitative titers can establish a baseline to evaluate treatment response. However, they require treponemal-based confirmation because detectable antibodies can be produced by other inflammatory conditions. Sensitivities vary depending on the type of test and stage of infection (Table 1), with lower sensitivities in primary syphilis and late syphilis [24]. False-positive test results are associated with viral infections, pregnancy, malignant neoplasms, autoimmune diseases, and advanced age [15, 25]. The specificities of the nontreponemal tests depend on the prevalence of biological false-positive test results in the population but are generally >95% [14].

**Early treponemal tests.** Before the enzyme immunoassays (EIAs), treponemal tests were used for confirmation after a reactive nontreponemal test. Treponemal tests available in the United States include the microhemagglutination assay for *T. pallidum* (MHA-TP), the *T. pallidum* particle agglutination (TPPA), the *T. pallidum* hemagglutination assay (TPHA), and the fluorescent treponemal antibody absorption assay (FTA-ABS). The MHA-TP and TPHA are also cleared by the FDA for screening of blood donors for syphilis. The MHA-TP uses sensitized sheep erythrocytes coated with *T. pallidum* (Nichol’s strain), which agglutinate with antitreponemal IgM and IgG antibodies [26]. The TPPA is based on agglutination with the same treponemal antigen as the MHA-TP but uses colored gelatin particles [16]. The TPHA test is a microhemagglutination assay for IgM and IgG antibodies [27]. The FTA-ABS uses fixed *T. pallidum* to bind IgM and IgG antibodies [14].

The FTA-ABS is considered the most sensitive method to confirm the presence of antibodies in early infection [28], but overall, the treponemal tests have lower sensitivities in primary syphilis compared with later-stage syphilis (Table 1). False-positive results are uncommon but occur in patients with collagen diseases, systemic lupus erythematosus, and other infections [29, 30]. Despite treatment, treponemal tests remain reactive for life except in patients treated early for primary syphilis [21].

**Rapid tests.** Development of rapid treponemal-based syphilis tests was driven by the need for simple, point-of-care tests in resource-poor countries. Although no rapid syphilis test has received FDA clearance, >20 are commercially available worldwide using serum, plasma, or whole blood specimens [31]. Most rapid tests detect IgM, IgG, and IgA antibodies [32] and involve immunochromatographic strips (ICSs) in which 1 or multiple *T. pallidum* recombinant antigens are applied to nitrocellulose strips as capture reagents [33] (Figure 1). Syphilis Fast (Disses Diagnostics) is a latex agglutination test in which the recombinant antigens are bound to latex particles [34].

Overall, rapid tests are highly sensitive and specific. The World Health Organization compared the performance of 8 rapid syphilis tests to a combined reference standard of TPHA/TPPA, reporting sensitivities of 84.5%–97.7% and specificities of 92.8%–98% [31, 35] (Table 2). Comparison of rapid tests among US sexually transmitted disease clinic patients demonstrated that fingerstick specimens were at least as good as venous samples for detection [36]. However, less sensitivity has been reported in other field settings with whole blood than with serum specimens [37, 38].

The advantages of rapid syphilis tests include their costs at $1–$3 per kit and availability of results within 5–20 minutes [31]. Rapid tests require minimal equipment and training, which is ideal for nonclinical settings. However, they cannot distinguish between active and treated syphilis, and false-pos-
Table 2. Treponemal Antigens, Antibody Targets, and Performance of Several Treponemal-Based Tests and Their Estimated Positive Predictive Values Based on Syphilis Prevalence Ranging from 0.7% to 4.0% in the US Population

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Treponemal antigens</th>
<th>Treponemal antibody targets</th>
<th>Reference tests</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive predictive value, %</th>
</tr>
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<tbody>
<tr>
<td><strong>Rapid tests</strong></td>
<td></td>
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<tr>
<td>Syphilis Fast [34]</td>
<td>Diesse</td>
<td>Recombinant (TpN15, TpN17, TpN47)</td>
<td>IgM, IgG</td>
<td>VDRL, TPHA, FTA-ABS</td>
<td>95.6</td>
<td>99.9</td>
<td>87.1–97.5</td>
</tr>
<tr>
<td>Determine Syphilis TP [31]</td>
<td>Abbott Laboratories</td>
<td>Recombinant (TpN47)</td>
<td>IgM, IgG, IgA</td>
<td>TPHA, TPPA</td>
<td>97.2</td>
<td>94.1</td>
<td>10.4–40.7</td>
</tr>
<tr>
<td>Espline TP [31]</td>
<td>Fujirebio</td>
<td>Recombinant (TpN15, TpN17, TpN47)</td>
<td>IgM, IgG, IgA</td>
<td>TPHA, TPPA</td>
<td>97.7</td>
<td>93.4</td>
<td>9.4–38.1</td>
</tr>
<tr>
<td>SD Bioline Syphilis 3.0 [31]</td>
<td>Standard Diagnostics</td>
<td>Recombinant (TpN15, TpN17, TpN47)</td>
<td>IgM, IgG, IgA</td>
<td>TPHA, TPPA</td>
<td>95.0</td>
<td>94.9</td>
<td>11.6–43.7</td>
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<tr>
<td><strong>Enzyme immunoassays</strong></td>
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<tr>
<td>BioElisa Syphilis 3.0 [43]</td>
<td>Biokit</td>
<td>Wild type</td>
<td>IgG</td>
<td>TPHA, FTA-ABS</td>
<td>99.5</td>
<td>99.4</td>
<td>53.9–87.4</td>
</tr>
<tr>
<td>CAPTIA Syphilis-G [44]</td>
<td>Trinity Biotech</td>
<td>Wild type</td>
<td>IgG</td>
<td>FTA-ABS</td>
<td>96.7</td>
<td>98.3</td>
<td>28.6–70.3</td>
</tr>
<tr>
<td>Eti-syphilis G [18]</td>
<td>Diasorin</td>
<td>Wild type</td>
<td>IgG</td>
<td>RPR, MHA-TP, FTA-ABS</td>
<td>99.4</td>
<td>100</td>
<td>58.4–89.2</td>
</tr>
<tr>
<td>Trep-Check IgG EIA [45]</td>
<td>Phoenix Biotech</td>
<td>Recombinant (not specified)</td>
<td>IgG</td>
<td>RPR, VDRL, TPPA, FTA-ABS</td>
<td>85.3</td>
<td>96.6</td>
<td>12.0–44.7</td>
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<tr>
<td>Syphilis EIA II [46]</td>
<td>Newmarket Laboratories</td>
<td>Recombinant (TpN15, TpN17, TpN47)</td>
<td>IgM, IgG</td>
<td>TPHA, TPPA</td>
<td>99.1</td>
<td>100</td>
<td>58.3–89.2</td>
</tr>
<tr>
<td>Syphilis Total [46]</td>
<td>Bio-Rad</td>
<td>Recombinant (TpN15, TpN17, TpN47)</td>
<td>IgM, IgG</td>
<td>TPHA, TPPA</td>
<td>97.4</td>
<td>100</td>
<td>57.9–89.0</td>
</tr>
<tr>
<td>Enzywell Syphilis Screen Recombinant [46]</td>
<td>Diesse</td>
<td>Recombinant (TpN15, TpN17, TpN47)</td>
<td>IgM, IgG</td>
<td>TPHA, TPPA</td>
<td>98.2</td>
<td>100</td>
<td>58.1–89.1</td>
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<tr>
<td><strong>Immunochemiluminescence</strong></td>
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<tr>
<td>LIASON Chemiluminescence Assay [47]</td>
<td>Diasorin</td>
<td>Recombinant (TpN17)</td>
<td>IgM, IgG</td>
<td>RPR, TPPA</td>
<td>95.8</td>
<td>99.1</td>
<td>42.9–81.6</td>
</tr>
<tr>
<td>Architect Chemiluminescence Assay [21]</td>
<td>Abbott</td>
<td>Recombinant (TpN15, TpN17, TpN47)</td>
<td>IgM, IgG</td>
<td>VDRL, TPPA</td>
<td>98.4</td>
<td>99.1</td>
<td>43.5–82.0</td>
</tr>
</tbody>
</table>

**NOTE.** EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption assay; MHA-TP, microhemagglutination assay; TPHA, Treponema pallidum hemagglutination assay; TPPA, T. pallidum particle agglutination.

* For tests with specificities of 100%, a lower estimate of 99.5% was used to calculate a range of positive predictive values considering the 95% confidence intervals around the reported specificities.
Figure 2. Composite results of syphilis testing algorithms using treponemal tests for initial screening and recommendations from the Centers for Disease Control and Prevention, 2008. Reproduced from the Centers for Disease Control and Prevention. §EIA, enzyme immunoassay (EIA). ¶Reactive with EIA treponemal test but nonreactive with rapid plasma reagin test. **Using Treponema pallidum particle agglutination or fluorescent treponemal antibody tests.

itive reactions can occur [39]. Positive results need confirmation with quantitative nontreponemal testing to determine recent infection and response to therapy.

EIAs. Veldkamp and Visser [40] recognized the potential for an automated T. pallidum enzyme-linked immunosorbent assay in the 1970s. Commercially available tests followed, along with an EIA to detect IgG antitreponemal antibodies using a microtiter plate of wells with wild-type T. pallidum antigens [41]. Compared with the TPHA and FTA-ABS, the EIA had a sensitivity of 98.4% and a specificity of 99.3% [41]. Subsequent EIAs used recombinant T. pallidum antigens instead of wild-type antigens. An immune-capture EIA (ICE Syphilis; Murex) that used recombinant TpN15, TpN17, and TpN47 had higher sensitivity than an EIA (Captia SelectSyph-G; Centocor) that used wild-type antigens (99% vs 91.4%; P<.01) [20]. An EIA that used 1 recombinant antigen (TpN44.5[a]) was reported to produce negative results after treatment [42]; however, the Captia SelectSyph-G and the Syphilis Fast test had a sensitivity of 95.7% in treated syphilis, demonstrating their ability to detect low antibody levels that may exist in treated and late latent infections [34].

EIAs reported in the literature have used different reference tests to determine sensitivities and specificities, precluding a direct comparison of their performance (Table 2). A comparative evaluation of 10 EIAs using either wild-type or recombinant T. pallidum antigens for antitreponemal IgM and IgG antibody detection demonstrated sensitivities of 94.7%–99.1% and specificities of 100% [46].

EIAs that detect only IgM antitreponemal antibodies have also been developed [47]. The Captia Syphilis-M EIA (Trinity Biotech) is cleared by the FDA for diagnosis of congenital syphilis [48] but may be applied for detection of primary infection in which it has a high sensitivity (Table 1) [19]. Although IgM antitreponemal antibodies may persist up to 18 months after treatment [34], the IgM EIA may be useful in monitoring treatment response in early syphilis [49]. The VDRL test result was negative 6–12 months after treatment of early syphilis in 48% and 70% of patients, respectively, compared with the IgM-EIA, which produced negative results in 71% and 92% of patients [50].

Since 2001, a few of the treponemal IgG EIAs, including the Captia Syphilis-G assay (Trinity Biotech), have been cleared by the FDA as both diagnostic and confirmatory tests [48]. An automated, multiplex flow immunoassay (Bioplex 2200; Bio-Rad Labs) is also cleared by the FDA, allowing antibody detection for autoimmune diseases and other infections (i.e., systemic lupus erythematosus, toxoplasmosis) in addition to the antitreponemal IgG [51]. The advantages of the treponemal
EIAs are their automation and ability to decrease personnel costs; however, other than the Captia Syphilis-M EIA, they are unable to distinguish treated from untreated infections.

**Immunochemiluminescence assays.** Automated syphilis assays based on chemiluminescence are available in which paramagnetic microparticles are coated with recombinant *T. pallidum* antigens and labeled anti–human IgG and IgM monoclonal antibodies are detected. The LIASON chemiluminescent assay (DiaSorin), which uses TpN17 as an antigen, had a sensitivity of 95.2% in primary or secondary syphilis [47]. The Architect Syphilis Chemiluminescence Assay (CLIA; Abbott) based on recombinant antigens (TpN15, TpN17, and TpN47) had a sensitivity of 98.4% for untreated syphilis and 97.5% for primary syphilis [21] (Table 1). The advantages of these tests are their high sensitivities in early syphilis and their high throughputs; however, like other treponemal tests, they cannot distinguish among recent, remote, and previously treated infections.

**TREPONEMAL SCREENING TESTS: A NEW PARADIGM**

The reversal of traditional syphilis algorithms using treponemal EIAs for screening has led to uncertainty in clinical management. The Centers for Disease Control and Prevention (CDC) evaluated the use of treponemal screening tests among 4 New York City laboratories [52]. Six percent of persons screened had positive treponemal ELISA results, of which 56% had negative nontreponemal test results and no history of prior treatment. Such results could reflect greater sensitivity of the treponemal EIAs for untreated syphilis, a high frequency of treponemal false-positive results, or some combination thereof. For situations involving positive treponemal ELISA results with negative nontreponemal test results, the CDC recommends use of a second treponemal test, such as the TPPA or the FTA-ABS (Figure 2). A positive test result confirms untreated syphilis, but if the second test result is negative, either no treatment or using a third treponemal test to “break the tie” is recommended. The CDC encourages clinicians to consider treatment for late latent syphilis in individuals with positive treponemal ELIA results to reduce the chance of progression to tertiary complications [52]. Future national guidelines will have to carefully consider how the new tests are to be deployed and their interpretation.

Important considerations with the new syphilis tests are their positive predictive value (PPV) and negative predictive value (NPV), which depend on the disease prevalence in the population tested. A study based on treponemal EIAs followed by RPR and TPPA confirmation (for specimens with a RPR titer <1:8) reported a US seroprevalence of 0.71% [53]. Seropositivity was highest among non-Hispanic blacks at 4.3% [53]. Therefore, the probability that the treponemal test result represents a true NPV when testing the US population is generally >98%. However, the probability that a positive treponemal-based test result represents a true PPV can be as low as 12% when screening in the United States (Table 2). The PPV can reach 90% as the syphilis prevalence or clinical suspicion increases in the population tested. Although some tests report sensitivities and specificities of 100%, perfection in biological tests is rare, and further experience in other populations may alter these results. The lack of a reliable gold standard for syphilis diagnosis is problematic, and some positive ELIA results can reflect false-positive reactions similar to other syphilis tests.

**SCREENING OF HIGH-PRIORITY POPULATIONS**

Few studies with the newer treponemal assays have focused on their use among high-priority populations, including persons infected with human immunodeficiency virus (HIV) or pregnant women. Among HIV-infected persons, the Determine Syphilis TP assay (Abbott) was reported to have a higher sensitivity (96.9%–99.2%) but slightly lower specificity (92.4%–95.5%) than in HIV-negative individuals [54]. The ICE syphilis ELIA apparently has a better performance than other treponemal EIAs for detecting both treated and untreated infections among HIV-positive persons [20]. Onsite (rapid) ICSs for syphilis screening resulted in a high proportion of correct diagnosis and treatment (89.4%) among antenatal patients in South Africa, compared with the on-site RPR test (63.9%) or off-site RPR/TPHA tests (60.8%) [55].

**COST-EFFECTIVENESS**

A principal question is the cost-effectiveness of treponemal-based screening for syphilis. In South Africa, which has a high syphilis prevalence, the cost-effectiveness of on-site ICS testing for averting congenital syphilis was $104 US dollars [56]. In resource-limited settings, use of rapid tests resulted in no loss to follow-up and higher treatment rates compared with laboratory-based RPR tests [57]. A Canadian study modeling a health systems approach of ELIA screening followed by treponemal confirmation estimated an incremental cost-effectiveness ratio of $461 Canadian dollars per correct diagnosis compared with standard RPR plus TPPA/FTA-ABS testing [58]. Cost-effectiveness assessments of treponemal screening algorithms in the United States will be imperative using populations with varying prevalences of treated and untreated infections.

**PUBLIC HEALTH IMPLICATIONS**

The CDC’s National Plan to Eliminate Syphilis identified the needs for expanded laboratory services and rapid screening in both medical and nonmedical settings [59]. The resurgence of syphilis in some US cities has involved men who have sex with men and individuals with high rates of HIV coinfection [60]. In those populations, rapid treponemal tests could be applied
for screening high-risk persons with difficulties in follow-up. However, programs using these tests also need access to quantitative nontreponemal assays for confirmation. Although rapid syphilis tests have been shown to be beneficial and cost-effective in antenatal patients in Africa, additional studies would assist in determining their applications in the United States.

Despite the advantages of the newer treponemal serologic tests for screening, publicly funded laboratories or those with low specimen volumes may opt to continue using nontreponemal screening tests to avoid the higher costs or complexity of the newer assays. Considering a ~20-fold increased cost for reagents between the RPR test versus the treponemal EIA (estimated $0.25 vs $5), programs need to weigh the benefits of EIAs based on their test volume and labor costs. Furthermore, the recommended algorithm for management of positive treponemal EIA results and negative nontreponemal test results may be problematic when faced with patient noncompliance with subsequent visits and the costs of repeat treponemal assays. Public clinics frequently evaluating patients with a high prevalence of previously treated syphilis may find treponemal-specific screening tests less cost-effective because of their inability to distinguish active from prior infections.

Highly sensitive treponemal EIAs will be beneficial for diagnosis of patients with suspected syphilis and no prior history, especially in early or late infections with nonreactive nontreponemal tests. A second treponemal test may not be necessary for diagnosis when the initial positive treponemal test result has a high PPV in individuals with signs or symptoms suggestive of syphilis. However, until formal assessments are conducted with diagnostic algorithms using treponemal-based assays, caution should be exercised in their interpretation.

Clinicians should be vigilant that different testing algorithms may exist as more laboratories shift to EIAs or other treponemal-based tests for screening. Because screening with treponemal-based tests cannot distinguish between treated and untreated syphilis, the medical history, including past treatment for syphilis, will continue to be crucial in distinguishing between these 2 possibilities. False-positive reactions will almost certainly occur with the treponemal EIAs, and this could create clinical management dilemmas that prompt either repeated testing on follow-up or unnecessary treatment. This problem will be greatest in routine screening of low-risk populations with low pretest probabilities of syphilis.

Since 1982, the World Health Organization has recommended both a nontreponemal and treponemal test for syphilis screening and diagnosis [61]. Syphilis guidelines in the United Kingdom now recommend screening with either an EIA or a combination of VDRL and TPHA tests, using IgM-specific EIAs when early primary syphilis is suspected [62, 63]. Other European guidelines for syphilis recommend either an EIA or TPPA as a screening test [64]. An evaluation of the public health impact of these guidelines will be necessary for directing future syphilis testing in the United States.

CONCLUSIONS

There have been notable advancements in the diagnostic tests for syphilis. New rapid ICS treponemal tests are beneficial in nonclinical settings because of their low cost, ease of use, and reasonable performance. Treponemal EIAs and chemoluminescence assays will be used increasingly because of their automation for screening large volumes of patients. In patients suspected of having syphilis, they will be a valuable clinical adjunct. Use in low prevalence populations will introduce new problems because some positive test results will be false positive. A fundamental knowledge of the limitations of these novel assays is imperative for clinical management.

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