survival, in patients with advanced HFrEF who were deemed to be dependent on a temporary mechanical circulatory support device or continuous intravenous inotrope infusion. These guidelines also provided a class 2a recommendation regarding durable LVADs for select patients with HFrEF and New York Heart Association class IV symptoms despite guideline-directed medical therapy to improve symptoms, functional class, and survival. Thus, a mandate emerges for the medical community to improve identification of ambulatory patients with advanced HFrEF and to develop processes to expeditiously refer patients who are potentially appropriate for destination therapy to advanced heart failure centers where the complex question about whether to proceed with LVAD implantation can be appropriately addressed.

The Critical Need to Modernize Syphilis Screening

Susan Tuddenham, MD, MPH; Khalil G. Ghanem, MD, PhD

In 2020, the rate of infectious (ie, primary and secondary) syphilis in the US was 12.6 per 100,000 and preliminary data from 2021 suggest even higher rates, estimated at 15.8 per 100,000. These rates have increased unabated since 2001 and are related to ongoing syphilis epidemics involving 2 populations: men who have sex with men (MSM) and heterosexual men and women. The latter epidemic has resulted in substantial increases in rates of syphilis among pregnant persons and, consequently, in the rate of congenital syphilis. The national congenital syphilis rate of 57.3 cases per 100,000 live births in 2020 is a 254% increase relative to the rate in 2016 and represents a serious failure of the US public health system.

In this issue of JAMA, the US Preventive Services Task Force (USPSTF) presents an updated Reaffirmation Recommendation Statement for syphilis screening in nonpregnant adolescents and adults along with an updated Evidence Report and Systematic Review that focused solely on the new evidence that became available since the 2016 recommendation. In the current statement, “the USPSTF recommends screening for syphilis infection in persons who are at increased risk for infection (A recommendation).” Screening (ie, testing in persons who do not have signs or symptoms) is one of the critical tenets in the control of communicable diseases, including sexually transmitted infections (STIs). Screening may result in increased identification of cases in the short term, but early detection and treatment over time should lead to enhanced syphilis control. Although the USPSTF has been promoting syphilis screening for years, uptake in key populations, such as people with HIV and MSM, has been poor, indicating the need for improvement.

Clinicians and patients must understand who should be screened and how often to do so. The updated USPSTF recommendation statement reaffirms that adults at increased risk for syphilis should be screened. The recommendation identifies MSM and people with HIV as populations at risk and recommends screening other patients for syphilis depending on a range of demographic, geographic, and behavioral factors. In terms

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In 2020, the rate of infectious (ie, primary and secondary) syphilis in the US was 12.6 per 100,000 and preliminary data from 2021 suggest even higher rates, estimated at 15.8 per 100,000. These rates have increased unabated since 2001 and are related to ongoing syphilis epidemics involving 2 populations: men who have sex with men (MSM) and heterosexual men and women. The latter epidemic has resulted in substantial increases in rates of syphilis among pregnant persons and, consequently, in the rate of congenital syphilis. The national congenital syphilis rate of 57.3 cases per 100,000 live births in 2020 is a 254% increase relative to the rate in 2016 and represents a serious failure of the US public health system.

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Clinicians and patients must understand who should be screened and how often to do so. The updated USPSTF recommendation statement reaffirms that adults at increased risk for syphilis should be screened. The recommendation identifies MSM and people with HIV as populations at risk and recommends screening other patients for syphilis depending on a range of demographic, geographic, and behavioral factors. In terms
of screening frequency, USPSTF suggests that MSM and people with HIV may benefit from screening up to every 3 months but does not define frequency for other groups. For example, at Johns Hopkins Hospitals in Baltimore, where the rates of infectious syphilis were reported to be 52.9/100,000 in 2019, sexually active people with HIV, MSM, and transgender women who have sex with men are screened at least annually and up to every 3 months, and people taking HIV preexposure prophylaxis at least every 6 months and up to every 3 months.\(^8\),\(^9\) Individually, individuals with a new sex partner, multiple sex partners, sex partners with concurrent partners, a sex partner with a recently diagnosed STI, individuals with a history of incarceration or transactional sex, and those with a history of methamphetamine, heroin, or injection drug use are screened at least once and up to every 3 months if risk factors persist.\(^7\) Screening also is offered to all individuals in clinical settings with high prevalence (eg, STI clinics), and at least 1-time testing is offered to all sexually active men younger than 29 years.\(^9\)

Knowing who and how often to screen is important but is unlikely to expand syphilis screening substantially. Individuals who need screening are generally young and otherwise healthy people who do not access the health care system consistently. Outreach strategies that target key at-risk populations, such as syphilis testing on mobile vans, have reported some local successes but have had a less obvious influence nationally.\(^10\) COVID-19 testing strategies that were implemented and broadly adopted during the pandemic offer a road map on how to expand screening for syphilis. For instance, this could involve having individuals (rather than clinicians) initiate the screening process by making screening easier and more convenient.

There are 2 main approaches for achieving this: at-home sample collection and at-home rapid testing.\(^11\),\(^12\) At-home sample collection allows patients to order, self-collect, and submit the samples via mail or a convenient drop-off location to a central laboratory for testing. In this model, the laboratory would conduct the testing, contact the individual with test results, and provide additional instructions (sometimes via affiliated clinicians) about next steps for management. The laboratory could also report positive results to the local health departments. This approach has been used for gonorrhea and chlamydia testing using nucleic acid amplification tests and has proved feasible and acceptable to patients.\(^13\),\(^14\)

At-home rapid testing, an even more convenient approach, could allow individuals to purchase an over-the-counter kit to collect a specimen and perform and interpret the test. Instructions included in these kits could help guide the next steps in management. Challenges with this approach include cost, accurate performance of test, interpretation of test results, connection to appropriate posttest care and counseling, and inconsistent public health reporting and follow-up, but technological solutions to these issues are possible. While these approaches are gaining widespread acceptance from patients and clinicians for other infections, their implementation for syphilis screening is complicated because syphilis diagnostics continue to present challenges.

Screening for syphilis, which has used the same approach since the early 20th century, requires the detection of 2 different types of antibodies: treponemal and lipoidal antibodies (“nontreponemal”—eg, the rapid plasma reagin). Treponemal antibodies confirm infection with syphilis and the lipoidal antibodies, through measured titers, provide information about management. For example, in persons with prior treated syphilis, a 4-fold or 2-dilution increase in titers suggests reinfection or treatment failure, whereas a 4-fold decline suggests an appropriate serologic response following treatment. While the interpretation of these results for patients without a prior history of syphilis is relatively straightforward, their interpretation for those with a history of syphilis is more complex because treponemal antibodies remain reactive lifelong for most individuals even after successful therapy,\(^15\) highlighting the necessity of lipoidal titers for managing infections. Treponemal and lipoidal antibodies also lack sensitivity in early infection when patients are infectious.\(^16\) The need for serologic specimens, the complexity of test interpretation, and the limitations in test performance during certain stages of infection highlight a critical need for better syphilis diagnostics. This will require a significant commitment of resources on a scale that can only be provided by the federal government through agencies such as the National Institutes of Health.

While awaiting better diagnostics, there may still be opportunities to optimize currently available technologies to expand screening of at-risk populations beyond the health care setting. Two point-of-care (POC) tests for syphilis are approved by the US Food and Drug Administration.\(^17\) Both detect the presence of treponemal antibodies in blood samples. They are limited by their inability to provide lipoidal titers and by concerns about lower test sensitivity, with estimates ranging from 50% up to 100% depending on the type of test, the setting, and the population tested.\(^17\) POC tests that detect both treponemal and lipoidal antibodies have been developed but are not yet approved by the US Food and Drug Administration (and their ability to provide lipoidal titers is limited). While these POC tests are usually performed by trained personnel, emerging data suggest that patient-directed self-testing using these products is feasible, acceptable, and could potentially expand access to syphilis screening.\(^18\) Despite the limitations of treponemal-only testing, a reactive treponemal-only POC test result could encourage at-risk individuals to interact with the health care system even if the test result represents prior treated infection rather than a new infection. Advances have also been described with at-home collection kits: Studies have shown the feasibility and accuracy of self-collected dried blood spots for syphilis testing, but those are also limited by the lack of lipoidal titers.\(^19\),\(^20\) Clearly, several challenges need to be addressed before syphilis screening could be expanded broadly outside of health care settings using POC tests and at-home collection kits, but solutions to these challenges are more accessible and would require fewer resources than those needed for the development of novel diagnostic approaches.

The updated USPSTF Recommendation Statement for syphilis screening is important, but relying on existing approaches that depend on traditional clinician-driven, clinic-based testing will not curtail the epidemic. Expanding access to screening through patient-initiated testing is a way forward.
This will require improved diagnostics, as well as addressing issues related to regulatory requirements, costs, and public health reporting. Industry, government, and academic collaborations to define regulatory requirements, identify stakeholder (e.g., patients, clinicians, regulators, funders, manufacturers, and commercial laboratories) needs and responsibilities, and develop a viable path to market have been initiated\(^\text{21}\) but need to be significantly scaled up. Funding should be prioritized for the development of novel syphilis diagnostics, just as there has been for development of syphilis vaccines, which are still many years from becoming a reality. Relying on emerging biomedical prevention interventions that hold promise, such as doxycycline postexposure prophylaxis, without concomitant robust screening strategies will not lead to syphilis control. Failure to modernize screening strategies for syphilis will also mean failure to control this infection.

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