Diagnostic and Resistance Testing for *Mycoplasma genitalium*: What Will It Take?

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(See the Major Article by Salado-Rasmussen and Jensen on pages 24–30.)

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*Mycoplasma genitalium* emerged on the scene in 1980, yet nearly 35 years later there is little agreement about its importance as a reproductive tract pathogen. Because of this disagreement and the lack of readily available diagnostic tests, there are no explicit testing recommendations and we still know relatively little about the population-level epidemiology of *M. genitalium* in most places. Further complicating this landscape are unacceptably high rates of treatment failure after standard regimens (30%–60%) [1, 2], suggesting that syndromic management does not adequately cover *M. genitalium*. Unlike most settings, the Statens Serum Institut in Denmark has offered *M. genitalium* testing since 2003 and macrolide resistance testing since 2007, allowing Danish clinicians to test for the organism and adjust treatment decisions as necessary. In addition to the clinical benefits, this provides a unique opportunity to track changes in the population-level epidemiology of *M. genitalium* over time. In this issue of *Clinical Infectious Diseases*, Salado-Rasmussen and Jensen summarize results of testing 31 600 specimens in Denmark over a period of 5 years [3]. In this relatively short time period, demand for *M. genitalium* testing doubled, prevalence increased, and macrolide resistance was nearly 40%. In light of these findings, Salado-Rasmussen and Jensen recommend that routine testing to simultaneously detect *M. genitalium* and macrolide resistance be incorporated into testing guidelines for sexually transmitted infections (STIs) so that treatment can be guided by etiologic diagnosis.

The approach they recommend is the current standard for diagnostic testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. High-risk patients presenting for care are routinely tested for these pathogens, systems to monitor the emergence of antibiotic-resistant *N. gonorrhoeae* have been in place for decades, and treatment recommendations for gonorrhea are modified when cure rates drop below 95% [4]. However, despite strong evidence that *M. genitalium* causes male urethritis, accumulating evidence suggesting it can cause pelvic inflammatory disease (PID) [5], and cure rates far below the 95% threshold, the question of whether routine diagnostic testing for *M. genitalium* should be recommended remains hotly debated. On the “pro” side are those who have weighed the evidence and conclude that the data provide reasonable evidence that *M. genitalium* can cause male and female genital tract disease. On the “con” side are those who have weighed the evidence, found it wanting, and demand stronger evidence for serious sequelae in women. This raises 2 important questions: (1) What degree of morbidity is required before recommending diagnosis and treatment of symptomatic disease, and (2) at what point is the evidence sufficient to make recommendations?

The demand for stronger evidence that *M. genitalium* can lead to adverse outcomes in women essentially ignores morbidity in men. Nongonococcal urethritis (NGU) is the most common male STI syndrome and accounted for >200 000 physician office visits per year the last time this was measured [6]. It likely accounts for more today. Treatment failures are not uncommon, and *M. genitalium* was the most commonly detected pathogen in several US cities, accounting for 33% of persistent cases [7]. If Centers for Disease Control and Prevention (CDC)–recommended therapies for NGU were effective against *M. genitalium*, the availability of testing would have little relevance.
However, doxycycline therapy is widely acknowledged to be ineffective against *M. genitalium*, and the high level of macrolide resistance reported by Salado-Rasmussen and Jensen [3] and others [8, 9] make azithromycin therapy equally unreliable. Moxifloxacin is currently highly effective against *M. genitalium* and, in the absence of diagnostic testing, is presumptively prescribed for persistent urethritis in some settings. However, the threat of resistance makes widespread use of this antimicrobial unwise, and a more judicious approach would be to reserve it for cases of known macrolide-resistant *M. genitalium* infection. However, most settings lack the ability to determine this.

In terms of sufficiency of the evidence, the ideal would be consistent evidence from several randomized controlled trials. In reality, this high standard is not always achievable. The studies “needed” to demonstrate a causal role of *M. genitalium* in PID, infertility, and ectopic pregnancy would require following untreated women over time, and the current evidence suggests that this would be unethical. Without historical cohorts, these types of studies cannot be done. In the absence of the studies we want, we must rely on the data from the studies we have. Although not unequivocal, the evidence for an association of *M. genitalium* with PID and infertility is moderate to strong [5]. Moderate evidence is sufficient for a US Preventive Services Task Force recommendation to offer or provide a service, and allows for inconsistency of findings across individual studies [10]. Although universal screening recommendations are not justified, implementing pairwise diagnostic and resistance testing would improve clinical care and may curb the spread of antibiotic-resistant *M. genitalium*.

The forthcoming update to the CDC’s STD treatment guidelines includes a new section on *M. genitalium*, providing specific guidance on treatment of *M. genitalium* infections for the first time. However, despite published protocols for several assays to detect both *M. genitalium* and macrolide resistance, the availability of systematic *M. genitalium* testing outside Denmark is extremely limited. Australia offers testing in at least 2 locations, but it is less available in the rest of the country. In the United States, validated tests are limited to research laboratories in large medical centers, and resistance testing is rarely done. Whereas the assay utilized in Denmark requires a 2-step process, Twin and colleagues have developed and validated a rapid high-resolution melt analysis assay to detect macrolide resistance mutations at the time of *M. genitalium* detection [11], enhancing efficiency. These 1-step and 2-step assays have already been implemented in Denmark and Australia, providing proof of concept, and could be implemented in other settings. Only the conviction that it is worth the investment is lacking.

Commercial laboratories in Britain and the United States, on the other hand, have recognized that there is a market for *M. genitalium* testing. Many have developed assays and begun marketing them to clinicians, as well as to the general public through self-testing kits. Whereas clinicians can leverage this mechanism, resistance testing is not incorporated and the performance characteristics of these assays are not publicized. Clinicians who order these tests must do so without knowing the accuracy of the assay and without clear guidance about what therapy is most appropriate in the event of a positive test result.

This conundrum has stimulated many to lobby diagnostic test manufacturers to bring a Food and Drug Administration (FDA)—approved assay for *M. genitalium* to market. Yet despite the earlier development of several well-validated, highly sensitive and specific research use–only assays, the substantial investment in time and resources required to secure FDA approval has proven too great an impediment. In the name of public health, we have identified creative ways to encourage the development of new treatments and diagnostics for other infectious diseases when the financial incentives for private industry are minimal. We should be able to do the same for a pathogen that causes known morbidity in at least half the population and has high rates of treatment failure. Targeted therapy based on etiologic diagnosis would enhance treatment outcomes and may stem the tide of emerging resistance. Salado-Rasmussen and Jensen’s recommendation to incorporate routine testing to simultaneously detect *M. genitalium* and macrolide resistance into STI testing guidelines is rational and should be our goal.

**Notes**

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**References**


