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As *M. Genitalium*, Gonorrhea Molecular Testing Expands, Antibiotic Resistance Assays May Follow

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3D illustration of *M. genitalium*

NEW YORK – Discovered only in the 1980s, *Mycoplasma genitalium* is more common than gonorrhea and has higher levels of antibacterial resistance in some populations.

But because it's relatively new sexually transmitted infection and can take up to six months to grow in culture, it is a less well-studied disease and its prevalence and pathology remain somewhat of a mystery.

Newly available US Food and Drug Administration-cleared molecular diagnostic tests, as well as in-development commercial tests to detect resistance, however, may soon enable a better understanding of the epidemiology of drug-resistant STIs like *M. gen* and gonorrhea.

But the market for the tests is unclear as such infections are typically more prevalent in disadvantaged populations — potentially making them less commercially attractive — and testing guidelines in the US have not been updated since 2015.

Antibacterial resistance is a growing problem for sexually transmitted infections, and *M. gen* and gonorrhea are no exceptions. Approximately half of *M. gen* infections are [resistant](#) to antibiotics in some parts of the world, including in the US, and increasing rates of drug-resistant gonorrhea is also raising alarms.

The US Food and Drug Administration-cleared molecular diagnostic tests to detect *M. gen* finally became available this year, from Roche and Hologic, and a test that detects genetic resistance markers in *M. gen* from Australia-based Speedx is now in the final stages of FDA submission. The firm is developing resistance tests for gonorrhea as well, while Hologic and Roche also have resistance testing in their pipelines.

Although selective pressure – in part caused by overuse of antibiotics - is leading both *M. gen* and gonorrhea to adapt evasion mechanisms, the two STIs are quite different in terms of what is known about them and in the response that has been mounted so far by health organizations to combat resistance.

For example, gonorrhea resistance has been the subject of research in the US for decades. The Centers for Disease Control and Prevention initiated the Gonococcal Isolate Surveillance Project ([GISP](#)) in 1986 to monitor resistance, and has since also launched an enhanced version of the project called [eGSIP](#). In 2016 CDC launched a project called Strengthening the United States Response to Resistant Gonorrhea (SURRG) to further enhance surveillance and conduct rapid investigations of outbreaks. Current [guidelines](#) also recommend gonorrhea and chlamydia screening annually in some asymptomatic populations.

Through these efforts, the most recent data show a quarter of the gonorrhea strains evaluated were resistant to tetracycline, 19 percent were resistant to ciprofloxacin, and 16 percent were resistant to penicillin. The minimum inhibitory concentration of azithromycin needed to combat the bugs was also creeping upward, with [new](#) azithromycin-attenuating mutations cropping up recently as well. Gonorrhea "superbugs" that are multidrug resistant are also an active area of investigation.

In contrast, much of *M. gen* is a riddle that remains unsolved. It is not a reportable infection, so it isn't entirely clear what the incidence is in the US, much less the rates of resistance, although the consensus seems to be that it is more common than gonorrhea — which has an estimated 800,000 infections in the US each year — and less common than chlamydia, which accounts for nearly 2 million infections.

The lack of knowledge is, in part, because of the nature of the bugs and lags in technology.

Parasitic gourd-shaped bacteria that latch onto epithelial cells in the urogenital tract, *M. gen* are the smallest self-replicating organisms on earth, with only the briefest of genomes. They're extremely difficult to culture — requiring up to six months and incubation on mammalian cell lines — so molecular methods are the best way to quickly diagnose infection.

Yet, *M. gen* has also been referred to as a [silent epidemic](#), with a prevalence as high as 20 percent in some low-resource settings.

Maria Trent, a physician and clinical researcher at Johns Hopkins University, explained in a recent interview that *M. gen* was only added to the CDC's STD treatment guidelines in the 2015 iteration. "It has been hard to predict the population impact because until recently there was not a commercially available test," she said.

Still, rates of antibiotic resistance in the US are high in the strains of *M. gen* that have been studied. Approximately half of all infections in one multicenter clinical [study](#) led by researchers at Hologic were resistant to macrolides, specifically azithromycin, the first-line antimicrobial that [CDC recommends](#).

There are also [dual-resistant strains](#) that are resistant to macrolides and quinolones, such that the antibiotic moxifloxacin is also ineffective. A study of 116 heterosexual couples in Alabama found an *M. gen* prevalence of 12 percent, with macrolide resistance rates of 60 percent and 11 percent of positive cases carrying dual-resistant strains.

Internationally, European [guidelines](#) issued in 2016 recommended molecular testing followed by resistance testing if available, and draft [guidelines](#) issued last year by the British Association of Sexual Health and HIV also recommended macrolide resistance testing of positive specimens, when possible.

In the US, there are no national screening recommendations for *M. gen*, and infection is not reportable to CDC. National STD [guidelines](#) issued in 2015 recommend nucleic acid amplification-based testing for *M.*

gen, but not resistance testing or testing patients after treatment to make sure they have actually been cured.

Update on commercial *M. gen* detection and resistance testing

Currently, only two molecular diagnostic tests have been cleared in the US for *M. gen* detection, from Hologic and Roche.

The Hologic [Aptima *Mycoplasma genitalium*](#) assay won *de novo* clearance earlier this year to become the first-ever US FDA-cleared *M. gen* test. It detects *M. gen* ribosomal RNA from urine, urethral, penile-meatal, endocervical, and vaginal swab samples collected in a clinical setting using the fully automated Panther system.

The Roche test, called [Cobas TV/MG](#), was cleared by FDA in May. It is a dual target test that detects both *Trichomonas vaginalis* and *M. gen* from symptomatic and asymptomatic patients, and it is cleared for use in urine, endocervical swabs, and vaginal swabs collected by clinicians or self-collected by patients in a clinical setting using the firm's Cobas 6800 and Cobas 8800 real-time PCR systems.

SpeeDx has also been [developing](#) its test for some time, and has established a presence globally, particularly in Australia. The firm [began clinical trials](#) of its *M. gen* resistance test last year and is [collaborating](#) with Cepheid to develop its *M. gen* resistance test on a new GeneXpert Flexible Cartridge.

Colin Denver, CEO at SpeeDx, said in an interview that the collaboration is progressing and the firms plan to officially launch a CE-IVD-marked test, called ResistancePlus MG Flexible, at the International Union against Sexually Transmitted Infections conference in Estonia this week.

In the meantime, while resistance seems to be a priority for both Roche and Hologic, firms are also waiting to see how this new market plays out.

At Hologic, Damon Getman, the director of diagnostic assay development, confirmed that the Aptima *M. gen* assay does not currently screen for antibiotic resistance.

"Our first priority was to bring a sensitive screening test through clinical validation and into the market to provide laboratories and healthcare professionals with a tool to identify this harmful infection," Getman commented in an email.

He noted that Hologic's test has been available as a research-use-only assay since the early 2000s, and its use has contributed to the current understanding of *M. gen*'s prevalence. "In all, our scientific team collaborated on or facilitated over 80 research publications over the course of the past 15 years, which have been seminal in building the case for *M. genitalium* as a serious health threat," Getman said.

The Hologic test has shown higher sensitivity than other testing in [some studies](#), which Getman said can be attributed to the relative abundance of rRNA compared to the DNA targets used by other tests, as well as the fact that many infections are low titer.

Another recent prospective multicenter study led by Charlotte Gaydos at Johns Hopkins looked at more than 3,000 patients and 11,000 individual specimens of various types also using the Hologic test. That study, which was published Sept. 5 in the [Journal of Clinical Microbiology](#), revealed a prevalence of symptomatic and asymptomatic infection of about 10 percent, and found that the Hologic test had sensitivities and specificities in the 90 percent range, in general, for the different sample types, although sensitivity was lower for endocervical swabs and female urine.

Hologic's research scientists are now working on antibiotic resistance tests, he said, although which antibiotic resistance markers to target is in flux. "We're looking forward to bringing innovation in resistance

testing for *M. genitalium* to the market as soon as possible," Getman said.

Roche's approach to *M. gen*, meanwhile, has been to design a dual-target test detecting DNA of *M. gen* (MG) and *Trichomonas vaginalis* (TV). Its test, which runs on the firm's high-throughput Cobas 6800 and 8800 systems, was cleared in May for male or female urine, endocervical swabs, and vaginal swabs collected by clinicians or self-collected by patients in a clinical setting.

Mario Torres, head of Roche Molecular Solutions, said in an email that the rationale for combining Trich and *M. gen* testing was that patients in some scenarios can have non-descript signs and symptoms and the combination "enables diagnostic flexibility for the clinician, as both can be ordered together or, if clinically warranted, they can request only TV or MG."

Torres said that labs see benefits in workflow consolidation and efficiency with its "complete STI menu" by running the TV/MG test in conjunction to its cleared *Chlamydia Trachomatis/Neisseria gonorrhoea* (CT/NG) testing, simultaneously on a single patient sample using its fully automated, high-throughput systems.

"As we continue to expand and fulfill our commitment to patient healthcare, MG is a critical part of the STI menu," Torres said, adding, "Macrolide resistance is a serious threat, and we are actively pursuing a solution to address this" on the Cobas 6800 and 8800 system menus.

But at SpeeDx, Colin Denver asserted that in populations with high levels of resistance, detection-only testing might actually be selecting for resistance if patients are given azithromycin as a first-line treatment.

Its ResistancePlus MG test, on the other hand, detects DNA of the bacteria as well as five markers of macrolide resistance from urine and swab specimens. It runs on open-platform instruments, and the firm plans to submit it for clearance initially to run on the ABI 7500 Fast Dx instrument.

Barbara Van Der Pol is an expert in STI testing at the University of Alabama at Birmingham School of Medicine who has managed the clinical trial for the SpeeDx. In an interview Van Der Pol said a platform-agnostic test like SpeeDx's is useful for certain settings because it can be adapted as a laboratory-developed test to any system that has open access capabilities. When the test kit is FDA-cleared it will give the confidence that the reagents have high sensitivity and specificity and the test could then be used on the Cobas Omni Utility Channel or use the Hologic Panther Fusion Open Access functionality, she said.

Van Der Pol also noted that she has been involved in many of the clinical studies for different *M. gen* assays. "Initially, I think people weren't really certain whether or not there would be any interest in a *Mycoplasma* diagnostic tool," she said, much less a diagnostic test that also incorporates resistance testing. And, STD's are "diseases of disparity," Van Der Pol said, with much of the testing for people at highest risk run at public health labs. As a result, economics is a big factor.

Denver said that SpeeDx has finished its clinical trials on the *M. gen* test and is hoping to submit in the next two months, with clearance possible in the first half of 2020.

The Hologic and Roche tests are "detection-only assays," Denver said, noting that in parts of the world where detection only-tests have been used and azithromycin was the main mode of treatment, such as in Australia, there has been a decline in cure rates.

Resistance-guided therapy is more of a personalized approach, he said, treating the patient based on the resistance markers that are present in their infection.

One recent study, published in *Clinical Infectious Diseases*, described a treatment regimen that incorporated empiric doxycycline and SpeeDx resistance testing, with azithromycin prescribed for infections that are susceptible and moxifloxacin prescribed for ones that were azithromycin-resistant. In a

part of Australia with high levels of resistance, this protocol boosted cure rates from about 50 percent to above 90 percent with little selection of macrolide resistance.

"It is a pretty spectacular result, using what are essentially already cleared, readily available, and cheap antibiotics to improve patient outcomes," Denver said.

To his mind, detection testing alone is essentially "identifying a population that is probably resistant and treating them with the antibiotic they are actually resistant to," which could unfortunately increase the amount of resistance in the population, he said.

At Johns Hopkins, Trent also said that molecular testing has the potential to advance diagnostic precision among populations facing the greatest STI health disparities and reduce the individual and population burden of disease. Also, "In an era of limited therapeutics, use of resistance assays has the potential to optimize antibiotic stewardship and develop protocols that actually work for patients," Trent said.

Her hospital's lab doesn't offer *M. gen* testing, but she is able to get it for her patients through Gaydos' research. "We are fortunate to have access to the currently available commercial product for *Mycoplasma genitalium* testing and another product undergoing FDA clearance for resistance testing through material transfer agreements related to our work," she said. The testing is performed under a research protocol, with retesting offered after a positive test at three months.

Update on commercial gonorrhea resistance testing, STI guidelines

SpeeDx also has a CE-marked [gonorrhea resistance test](#) designed to be a secondary test for CT/NG samples that were NG positive. It was adapted from a [PCR assay](#) developed by researchers at the University of California, Los Angeles, and the company continues to collaborate with researcher studying gonorrhea superbugs.

The Resistance GC test detects whether the gonorrhea bacteria is susceptible to ciprofloxacin, since empiric treatment with that particular drug has led to an increase in resistance, driving rates to about 30 percent, Denver said.

On the other hand, ciprofloxacin has the advantage of being an oral antibiotic that cures gonorrhea in a single dose in 70 percent of cases, and using it could avoid potential knock-on effects if a patient were instead given empiric azithromycin and happened to have an *M. gen* co-infection, he said.

Gaydos noted that the rates of drug-resistant gonorrhea are still rising, and there have been a handful of cases in the world that are untreatable. The CDC used to recommend azithromycin but now the consensus seems to be to treat gonorrhea with ceftriaxone in order to avoid increasing the resistance, she said.

Sancta St. Cyr, a medical officer within CDC's Division of STD Prevention, said in an email that the agency is currently evaluating available data and research related to the recommended treatment regimen for gonorrhea, to evaluate if changes are needed, but no decisions have been made at this time.

"Over time, gonorrhea has become resistant to nearly every class of antibiotic drugs used to treat it," St. Cyr said. Resistance to ceftriaxone has remained low in national surveillance, suggesting that gonorrhea is still effectively treated by this antibiotic in the US, but for certain antibiotics, like ciprofloxacin, resistance increased from about 9 percent in 2009 to 30 percent in 2017, St. Cyr also said.

In 2015, CDC's STD treatment guidelines changed to recommend only one regimen of dual therapy for the treatment of gonorrhea – injectable ceftriaxone, plus oral azithromycin. "Emerging resistance to ceftriaxone has not been seen since the dual therapy approach was implemented," St. Cyr said, adding that there has not yet been a confirmed treatment failure in the US when using this therapy.

For *M. gen*, dual resistance to azithromycin and moxifloxacin leaves few options besides experimental treatments, Gaydos said, and some desperate patients have been reaching out directly to researchers. "We've had numerous emails asking, 'Please, help me,'" Gaydos said, noting that she does her best to refer these cases to treatment experts.

Trent has also been contacted by patients with resistant *M. gen* or allergies to antibiotics. "One patient suggested that they would be willing to travel overseas to obtain access to an antibiotic available in Europe," she said, but, "The reality is that most patients do not have the means to seek care outside of the US healthcare system."

Overall, whether there is enough evidence in the US to recommend changing *M. gen* testing and treatment guidelines is unclear. Trent noted that there are few randomized controlled trials examining longitudinal clinical outcomes for various treatment approaches among asymptomatic and symptomatic patients, and no population-based data to help drive decision-making.

"What we do have are high-quality pockets of data associating *Mycoplasma genitalium* infection with adverse reproductive health outcomes in selected populations across the country," she said.

Van Der Pol said that in Australia the guidelines now indicate treating cases of urethritis that are not due to gonorrhea with empiric doxycycline rather than azithromycin, in order to cure chlamydia, if it is present, but the guidelines also recommend to test for *M. gen* as well as resistance.

"If you're diagnosing the disease but you're not treating it based on a resistance profile, you may actually be helping to cause the problem," she said.

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