New test is first in US to help detect new STD threat

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It is hard to get much of a reputation if nobody knows you're around, and that has definitely been the case for *mycoplasma genitalium*, the tiny bacteria estimated to be more prevalent than the bug that causes

gonorrhea but is almost completely off the public's radar.

That's because, until very recently, it has been difficult for front-line physicians to confirm that this particular microbe—the smallest bacteria ever detected—was present in specific patients.

However, that situation is likely to change due in large part to the work of the sexually transmitted disease division of Hologic Inc. Based in San Diego and formerly known as Gen-Probe, the company that revolutionized automated blood testing for infectious diseases such as HIV and hepatitis B and C, Hologic was the first in the nation to get a *mycoplasma genitalium* test approved by the U.S. Food and Drug Administration.

Hologic didn't get the field to itself for long. In late May, the FDA approved its second *mycoplasma genitalium* test application for Roche, the Swiss multinational pharmaceutical and diagnostic giant. A third entrant made by an Australian company called SpeedDx is seeking accelerated approval for its own test, which can also detect whether *M. Gen.* infections are resistant to antibiotics.

Compared to more familiar sexually transmitted diseases, *M. Gen.* is a newcomer. The U.S. Centers for Disease Control and Prevention identified the microbe in 1980, but didn't declare it an "emerging issue" until 2015.

According to the CDC, *M. Gen.* infection is the cause of between 15% and 30% of recurrent urethral inflammation cases in men and about 30% of cervical inflammation cases. Some studies have also suggested that *M. Gen.* infection contributes to infertility, pelvic inflammatory disease in women and birth complications, though the evidence is not yet considered strong enough to constitute scientific proof.

The new availability of FDA-approved testing, however, may help researchers get closer to understanding all of the ways this mysterious microbe affects the humans it calls home.

Lisa Manhart, a professor of epidemiology at the University of Washington School of Public Health and one of the world's foremost experts on *mycoplasma genitalium*, said having an FDA-approved test makes it more likely that clinicians will determine whether it is M. Gen, rather than another bacterium such as chlamydia trachomatis, that is causing an infection.

"You tend to see greater adoption when you have an FDA-approved test, because FDA approval signifies that it has been through a very rigorous process and has been very well validated," Manhart said.

She added that testing could help future observational studies seeking to more firmly link pelvic inflammatory disease in women to *M. Gen.* infection. In severe cases, pelvic inflammation can cause infertility. But more studies are required to prove that this microbe has significant reproductive consequences. The few studies that have attempted to link the two, she said, have been small and observational, meaning that, while they can show correlation, they can't prove definitively that one causes the other.

"It's very hard to draw conclusions about infertility, especially in women, at this time," Manhart said.

In order to prove that the test works, researchers collected nearly 12,000 specimens from 3,300 patients, comparing the results to three different research assays. The result: Depending on the type of sample collected, Holigic's M.Gen diagnostic's ability to detect *M. Gen.*"s presence ranged from 77.8% to 99.6%. Results were more consistent at proving that *M. Gen.* was not present, achieving that result between 97.8% and 99.6% of

the time, with female urine and male urethral and urine samples proving best for ruling infection out.

And that's by design said Damon Getman, Hologic's senior principal scientist and director of research and development. Sitting in the soaring atrium of a building on Hologic's sprawling San Diego campus, the molecular biologist with a doctorate in pharmacology explained that creating a medical diagnostic test is always about finding the right balance between specificity and sensitivity. Sensitivity is a test's ability to detect the presence of an organism while specificity is its ability to rule infections out.

Given that there are significant social consequences to telling a person that they have a sexually transmitted disease when they don't, Getman said the test was specifically designed to emphasize specificity.

"There is no perfect test with perfect specificity and sensitivity," Getman said. "We always are in a situation where we have to use imperfect tools in situations that demand perfection, and you have to decide, do you not want to miss an infection, or do you never want to have a false positive? That question requires you to think very carefully about where to shift your emphasis."

That balance boils right down to test design.

There are many types of mycoplasma bacteria that commonly reside inside the human body, and most don't appear harmful. The diagnostic tool uses ribonucleic acid, the relatively short but powerful snippets of genetic code inside cells' ribosomes, to detect *M. Gen.*"s presence through an innovative replication process pioneered in San Diego by Gen-Probe, which Hologic purchased in 2012.

RNA, unlike DNA, Getman explained, is quite plentiful in *M. Gen.* with

about 1,000 copies inside each cell. But, comparing the sequence of *M. Gen.*"s RNA to that of other mycoplasma bacteria shows that there is very little difference. Differences may be only a few of the paired molecules, called base pairs, that make up a much longer genetic sequence.

Here, at the molecular level, is where scientists design special "probes" and "primers" that will bond specifically to the sites within M. gen's RNA that make it slightly different from other species of mycoplasma that might be present.

These tiny tools are able to zero in on extremely tiny targets. In the case of Hologic's M. gen test, Getman said, the area used for detection was only about 80 nucleic acid base pairs long out of a larger string of more than 500,000.

Given that small primers are less likely to stick to their targets than large ones are, researchers knew that the test might miss some infections. But, at the same time, such a tight focus on just the very spot that makes *M. Gen.* different from other mycoplasmas also meant it was much less likely that a primer would connect with a benign bacteria, significantly reducing the risks of a false positive.

"That gave us this razor-sharp selectivity for just that particular organism," Getman said.

It took surprisingly little time—just a few months—to select the right target and design the molecules necessary to make the text work. The team had an initial design functioning well enough to publish a preliminary paper back in 2006. However, that was just the beginning. It took more than a decade to evaluate the function of what they had created, working with academic researchers to use the tool with different types of patients, building a knowledge base of which patients were most

likely to benefit from being tested.

A serious scientist with more than 20 years in his field, Getman is not prone to giddy superlatives. But he can't contain the sheer joy of creation, of getting to see something new move from design through testing to the real world where it can help detect an emerging threat.

"Doing this work, it really is a lot of fun," he said, grinning like a kid on Christmas morning.