WhitePaper

Molecular Testing for Urinary Tract Infection (UTI):

2020 Update on Clinical Utility and Reimbursement Trends

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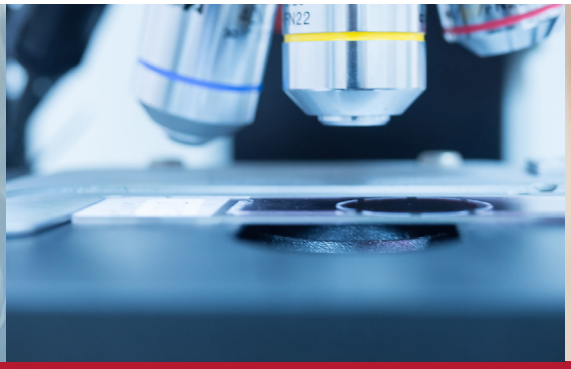

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Introduction

Urinary tract infection (UTI) is the second most common type of infection in the US, accounting for 10.5 million office visits per year and 50 percent of all Medicare hospital admissions.[1, 2] UTI is among the most common cause of bacterial infections in long-term care facility residents.

Effective treatment of a UTI depends on the accurate identification of the pathogen(s) and the correct choice of antibiotic(s).[3] Although culture-based clinical laboratory testing methods remain the gold standard for diagnosing UTI in both research and clinical laboratories, the clinical utility of such methods continues to be called into question.[4]

About 60 percent of all women will develop a UTI during their lifetime.[5] Of those, 25 to 30 percent are likely to have a repeat infection.[6] These infections can be devastating. Complicated or untreated UTIs frequently cause sepsis in older adults above 65 years of age, with mortality ranging from 25-60%.[7] About 50 percent of all sepsis cases among nursing home residents originate from UTIs.[8]

"When you look at that, you start to get an understanding of the significance of the problem," says David Baunoch, PhD, Chief Scientific Officer at Pathnostics, which has conducted several clinical trials using a rapid molecular test to determine whether a UTI test that analyzes DNA performs better than traditional culture-based tests.[9]

This white paper explains the experiences of early adopters of rapid molecular testing for UTI, provides an update on the status of clinical utility of these tests, and describes healthcare settings where molecular testing for UTI is expected to be of value to improving outcomes.

Chapter 1:

Problems and Limitations of Culture-Based Testing for UTI in Contrast to Molecular Testing

Current culture-based methods for detecting UTI pathogens have several limitations. Those limitations include subjectivity and specificity, length of time to results, and missed positive samples.

Culture-based methods of identifying uropathogens are dependent on whether or not the pathogen can grow on an agar plate. These tests are performed by placing a drop of urine on a culture plate and incubating it overnight. The culture-based test determines positive or negative based on the presence or absence of uropathogens the following morning.

"It's really a biased result," Baunoch said. "It's inherently based on whether or not the particular group of organisms can grow out in that cultural medium in the required time. The problem really comes down to the fact that a large number of Gram-negative and especially Gram-positive organisms cannot grow in those culture conditions."

"First, we look at the test in general: a traditional culture test for UTIs. If you're 30 percent false negative, you know you have a significant problem," Baunoch said. "It's not only a false negative that's important. It's also the number of additional organisms that are missed."

Properly implemented and applied, molecular diagnostic technologies enable the microbiology laboratory to determine a positive infection, the type of infection, and what will treat that infection, with shorter turnaround time than traditional culture-based testing methods.[10]

UTIs are often polymicrobial, meaning that multiple uropathogens are

responsible for the diagnosis. A recent study[11] that compared traditional urine culture testing to multiplex polymerase chain reaction (PCR) molecular testing, run in parallel, showed that the molecular method found six additional polymicrobial cases for every one found using urine cultures, explained Baunoch.

The multiplex panel used in the study tested for 31 bacteria, and PCR and urine culture together identified 29 different bacterial pathogens. PCR detected 24 bacteria, while culture detected 21 different bacteria.

"Molecular methods have extreme sensitivity and specificity that allow for the identification of additional pathogens that are missed," Baunoch explained. "This becomes an issue especially in these patients who are being hospitalized with urosepsis. They often tend to be complex infections with multiple organisms present."

Raj Patel, MD, President and Chief Medical Officer at Associated Urological Specialists in Chicago, explained the adoption of molecular testing in his practice.[12]

Clinicians were aware that culture-based tests were not 100 percent effective in identifying bacteria that could cause infection, Patel said. That especially was true for prostatitis, he said, where a patient had symptoms likely related to an infection, but the urine culture would not identify the organism. Culture-based tests also did not pick up infections in patients who had been exposed to antibiotics.

But, Patel said, "We didn't realize how far off the mark we were until the PCR-based studies, as well as our own experience in seeing men and women who have recurrent infections and seeing the true culprits identified in the PCR-based tests."

Patel's team also saw patients who had already been on antibiotics; no bacteria grew in culture. "In those cases, they may be treated with multiple broad-spectrum antibiotics intravenously until a certain time period or if we're able to find out exactly which bacteria it grows out," he said.

Associated Urological Specialists began using the PCR-based molecular test in 2016.There, the test is already standard practice in cases of complicated UTIs, men and women over the age of 60, recurrent infections, patients who are on steroids or have diabetes, or those who have stones.

Associated Urological Specialists consists of a group of 17 physicians who order 200 to 300 molecular tests per month.

"In the simple setting, we still use urine culture. At this point, we're selecting only patients who we think have complicated UTIs or features that would put the patient in more harm if we didn't identify the correct bacteria right from the get-go."

—Raj Patel, MD
President and Chief Medical Officer, Associated Urological Specialists

Chapter 2:

Recent Clinical Trials Focused on UTI Diagnostics Using Rapid Molecular Testing

Rapid molecular tests are emerging as a strategy for controlling the impact of infectious diseases. New diagnostic methods may be promising.

One such test is the PCR-based Guidance UTI test which consists of both multiplex-polymerase chain reaction (M-PCR) and pooled antibiotic susceptibility testing (P-AST). The test is explained as simultaneously diagnosing and guiding antibiotic treatment for recurrent, persistent, or complicated UTIs. According to Baunoch, Guidance is affiliated with $4 million worth of clinical trials and has been used in well over 100,000 patients.

For example, an article published in the February 2020 edition of *Urology*[13] explains the results of a 582-patient retrospective trial. The study showed that multiplex PCR is not inferior to traditional urine culture, and in fact detected bacteria in 36% of symptomatic patients who had a negative urine culture.

In addition, multiplex PCR detected more polymicrobial infections than urine culture (in 28% of patients compared to 7% of patients). In addition to higher detection rates, PCR can provide results in as little as 6 hours, while cultures take 48 or more hours. The rapid, accurate identification of uropathogens offered by PCR can facilitate more appropriate and efficacious treatment and may improve clinical care and outcomes.[14]

In 2020, Pathnostics expects to publish the results from two additional trials, one consisting of 511 patients and the other of

66,383 patients, according to Baunoch. Georgia-based Capstone Healthcare will also begin working on a large study with Pathnostics and Thermo Fisher.

When Capstone Healthcare began molecular testing for UTIs in August 2018, they worked with one small urology group. Now, in addition to urology, Capstone works with urgent care clinics, long-term care, family practice, pain clinics, and a wide range of providers. Capstone has also expanded the number of microorganisms and antibiotic resistance genes in the UTI test.

Capstone describes its Molecular UTI test as an optimized UTI panel that looks beyond the culture.

"We started out looking at 17 organisms. Within a year and a half, use of molecular testing was applied to antibiotic resistance genes, sexually transmitted infections, and antibiotic treatment charts were added. It's ever-evolving and as a result of the progress, test demand and volume have grown."

—Trisha Lauterbach
Director of Laboratory Operations,
Capstone Healthcare

Capstone conducts its own in-house testing, describing the service as an optimized UTI panel that offers rapid turnaround time compared to traditional microbiology techniques. For the first six months of use, Capstone compared the sensitivity of every molecular test to a culture-based test, run in parallel.

"Specifically with our molecular UTI tests, we currently look at 39 of the most common pathogens that we see in our patient population that contribute to urinary tract infections and antibiotic resistance gene markers for 10 classes of antibiotics," explained Trisha Lauterbach, Director of Laboratory Operations for Capstone Healthcare.[15]

"We use an antibiotic treatment chart on our report that shows which microorganism and antibiotic resistance genes have been detected," Lauterbach said. "The report provides antibiotic recommendations based on commonly used antibiotics to treat the infection and takes into account any antibiotic resistant genes detected."

"By using molecular PCR, we are able to identify micoorganisms that traditional culture cannot, such as fastidious organisms and STI," Lauterbach said." We can also identify individual microbes in polymicrobial infections, providing the physician valuable information to make treatment decisions."

Turnaround time is an important consideration for researchers looking to enhance the quality of patient care. In this case, the importance of the shortened time to results and start of treatment cannot be overstated in the value of molecular diagnostic tests.

Capstone Healthcare runs about 1,000 molecular UTI tests each month and aims for a 24-hour turnaround time, Lauterbach said,

although, "our average turnaround time right now is about seven hours from the time we receive the sample here at the laboratory." Treatment options at the physician's disposal are much greater when they get information at the point of care rather than waiting from three to five days to get results, she said.

In the case of Patel's Associated Urological Specialists, which maintains an in-house laboratory, the turnaround time for test results is usually within 24 hours, according to Patel.

"We don't have to treat empirically and wait like we do with urine culture where it can take two to three days, and sometimes we can't even identify the exact or all the bacteria that cause issues," Patel said. "We see a significant improvement in tailoring the care and being much more selective on which antibiotics are appropriate to use on the patients with these infections."

Patel sees practical, useful applications of the molecular test, especially for older patients who are dependent on others for transportation and may not be able to get to a clinic. For this population, an untreated infection left to progress can cause other health issues and hospitalization.

A patient can begin antibiotics based on symptoms, then provide a sample within five days. The molecular test is sensitive enough to identify the causative agent(s)—even though a patient is on antibiotics. If used with urine culture, more often than not, the presence of antibiotics in those bacteria won't allow bacteria to grow on the culture immediately, Patel explained.

Added Baunoch, "While the molecular test provides initial information, a phenotypic test is used to ask the question 'does that organism actually respond to the antibiotic or not.'"

Chapter 3:

Reimbursement Trends and Cost Versus Value in Molecular Testing for UTI

Insurers and other payers have acknowledged the benefit of molecular diagnostic testing, which includes deoxyribonucleic acid-(DNA) or ribonucleic acid-(RNA) based analysis (with or without amplification/quantification). This is because of the sensitive, specific, and timely identification of organisms (relative to that of traditional culture-based methods).

A minireview in the *Journal of Clinical Microbiology* explains that "selecting the right test for the clinical setting involves the evaluation of test performance, laboratory feasibility, and cost versus value. To ensure that the diagnostic technology selected is appropriate for the clinical setting, it is important to consider testing volumes, diagnostic yield, and the feasibility of performing the test in the laboratory setting."[16]

Additionally, "While a simple analysis can be used to compare costs and charges for existing diagnostic tests versus new rapid diagnostic tests, a true cost-value analysis should include "back-end" cost savings of decreases in resource utilization (antimicrobials, unnecessary admissions, and lengths of stays), as well as effects on morbidity and mortality rates."[17]

In the case of molecular testing for UTIs, the higher payer cost of molecular assays must be considered alongside the value of potential downstream savings and improvement in the patient's quality of care.

UTIs have just over a $13 billion impact on the healthcare system in general, so when you look at costs, it is important to first understand the true impact, Baunoch said.

For patients, the problem is not only the UTI itself but the threat of urosepsis, which is a complication of UTI. More than half the cases of urosepsis among older adults are caused by a UTI, according to the Sepsis Alliance, a charitable advocacy organization.[18]

A Spring 2020 release of research published in the *JOJ Urology and Nephrology* explains that utilization of M-PCR and P-AST or urine specimens was associated with at 13.7% decrease in hospital admissions and/or emergency department utilization when compared to the use of standard urine cultures (SUC) testing. The utilization results that were reported occurred during the course of home-based primary care.[19]

Patel suggests that outpatient settings and assisted living facilities will benefit similarly.

Adds Baunoch, the application may be of value to long-term care facilities particularly.

Despite the potential benefits of M-PCR and P-AST testing, payment denials and delays are significant concerns. Such tests may require prepayment medical review but may be covered by Medicare, and in some states, by Blue Cross and other private payers.

Molecular-based tests are reimbursed at a higher rate compared to the traditional, economical standard culture. The advantage is in appropriately diagnosing the patient to ensure right treatment at the right time, Baunoch said.

"We pay close attention to reimbursement trends. Commercial [insurance] and Medicare both continue to reimburse," said Lauterbach. "As more of us are conducting clinical studies and showing the true clinical utility and validity of the testing, it will continue to be reimbursed and continue to be used in clinical practice."

Conclusion

Molecular tests are becoming more routine as diagnostic tools, with many now covered by Medicare and commercial insurers. In certain circumstances, molecular diagnostics may be positioned to become standard tests.

Toward urinary tract infection, UTI-related urosepsis, and reducing the related healthcare costs of both, there is a growing body of evidence around real-time polymerase chain reaction (RT-PCR) technology. Molecular tests based on PCR technology identify uropathogens traditionally missed by culture-based tests.

Driven by urgent, unmet analytical and clinical care needs, the adoption of the rapid molecular test—particularly RT-PCR for urinary tract infection control and treatment—has important implications for home-based primary care, as well as assisted living and long-term care facilities, and the hospitals that serve these patient populations.

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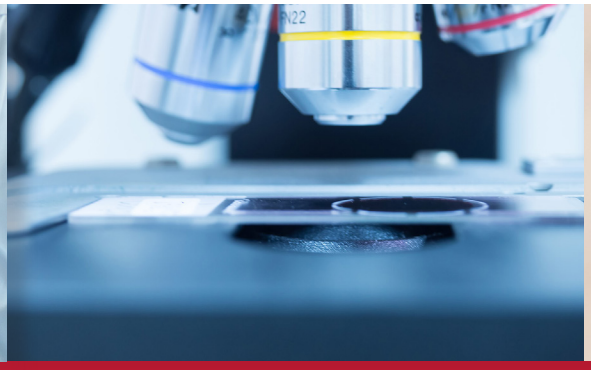

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