Anthem

Medical Policy

Subject: Combined Pathogen Identification and Drug Resistance Testing
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Description/Scope

This document addresses combined pathogen identification and drug resistance testing, including pooled antibiotic sensitivity testing (P-AST). This type of test involves a combination of Multiplex Polymerase Chain Reaction (M-PCR) assay for the identification of pathogens in a biological sample with genotyping for antibiotic resistance genes. This type of testing has been proposed for the treatment of recurrent, persistent, and complicated urinary tract infections (UTI) and other conditions that have been refractory to conventional pharmacotherapy.

Position Statement

Investigational and Not Medically Necessary:

Combined pathogen identification and drug resistance testing is considered **investigational and not medically necessary** in the outpatient setting for all indications.

Rationale

Combined pathogen identification and drug resistance testing involves genetic identification of specific pathogens and antibiotic resistance genes in a biological sample with M-PCR, with or without phenotypic analysis of antibiotic resistance. This type of testing has been proposed to assist in the treatment of recurrent, persistent, and complicated infections refractory to conventional treatment. A number of such assays have become available for identification of multidrug-resistant bacteria and fungi. However, to date such assays have been limited to the detection of a few specific genetic resistance targets in a given bacterial species. For many bacteria, antimicrobial resistance is complex, and molecular assays that target only a few known resistance genes to predict antimicrobial susceptibility are insufficient and possibly misleading. Detection of specific genetic resistance targets is further complicated by the emergence of genetic variants. Genotypic results do not obviate the need for phenotypic antimicrobial susceptibility testing, which is still necessary to confirm test results and to provide information about other possible therapeutic options. Molecular testing is customarily performed in addition to, not in place of, phenotypic antimicrobial susceptibility testing.

Urinary tract infections (UTIs)

Combined pathogen identification and drug resistance testing, using the P-AST assay was initially developed to assist in the treatment of complicated UTIs where the infection has been resistant to conventional antibiotic therapy. The first test to market using this technology was the Guidance® UTI (Pathnostics™ Inc., Irvine, CA), which was proposed as an alternative to techniques commonly used to detect bacterial nucleic acid sequences that confer antibiotic resistance, such as PCR and DNA hybridization.

UTIs are considered complicated when there is an increased chance for a complicated course, for example in pregnant individuals, individuals with anatomic or functional abnormalities, those with long-term indwelling urinary catheters, renal diseases, and immunocompromising diseases (Bonkat, 2018). For complicated UTIs, Escherichia coli (E. coli) is the most common cause, but other causative uropathogens include other enterobacteriaceae, pseudomonas, enterococci, and staphylococci (methicillin-sensitive staphylococcus aureus [MSSA] and methicillin-resistant S. aureus [MRSA]) (Hooton, 2018; Gupta, 2018).

In 2018, the European Association of Urology (EAU) released an update to their Urologic Infections guideline in which they state (all with a ‘Strong’ strength of rating):

Do not screen or treat asymptomatic bacteriuria in the following conditions:

- Women without risk factors;
- Patients with well-regulated diabetes mellitus;
- Post-menopausal women;
- Elderly institutionalized patients;
- Patients with dysfunctional and/or reconstructed lower urinary tracts;
- Patients with renal transplants;
- Patients prior to arthroplasty surgeries;
- Patients with recurrent urinary tract infections.

The EAU document recommends:

- Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa (‘Strong’ rating).
- Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment (‘Weak’ strength of rating).
- Diagnose recurrent UTI by urine culture (‘Strong’ rating).
- Recurrent UTI indicates that the occurrences are symptomatic.
- Use laboratory urine culture to detect bacteriuria in patients prior to undergoing urological interventions breaching the mucosa (‘Weak’ rating).

The EAU defines complicated UTI (cUTI) as occurring:

> In an individual in whom factors related to the host (e.g., underlying diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g., obstruction, incomplete voiding due to detrusor muscle dysfunction) are believed to result in an infection that will be more difficult to eradicate than an uncomplicated infection. Other factors associated with cUTIs include: vesicoureteral reflux, recent history of instrumentation, UTI in males, pregnancy, and healthcare-associated infections. Laboratory urine culture is the recommended method to determine the presence or absence of clinically significant bacteriuria in patients suspected of having a cUTI (Bonkat, 2018).

Results from a large multi-national study of 4264 women from 10 countries, the Antimicrobial Resistance Epidemiological Survey on Cystitis (ARESC), showed that up to 10.3% of E. coli in UTIs are resistant to at least three different classes of antimicrobial agents with ampicillin having the highest degree of resistance (48.3%) (Schito, 2009).

To date, studies of combined pathogen identification and drug resistance testing of urine have been insufficient to demonstrate clinical utility. In 2020, Daly and colleagues reported on a retrospective study of existing data from 66,383 individuals seen for possible UTI by house-call primary care providers. Trial participants were divided into two cohorts. One cohort was treated based upon the results from standard urine cultures (SUC). The other cohort was treated in accordance with results from an assay combining M-PCR and P-AST of urine specimens. The total number of emergency department visits and hospitalizations were compared between the two cohorts. The investigators found that the use of the combined M-PCR/P-AST was associated with a 13.7% decrease in hospital admissions and/or emergency department utilization when compared to the use of SUC testing (3.27% vs. 3.79%; p=0.003). The investigators concluded that these findings suggest that use of a combined M-PCR/P-AST assay in outpatient management of suspected UTI may improve patient outcomes and reduce emergency department and hospital utilization. The investigators noted that randomized studies are underway to investigate further the role that M-PCR/P-AST may play to aid in the management of UTI in the elderly population (Daly, 2020).

In 2020, Vollstedt and colleagues collected urine specimens from 3124 individuals with symptoms of UTI. Of these, M-PCR testing detected bacteria in 61.1% (1910) of specimens. P-AST results were available for 70.8% (1352) of these positive specimens. Of these positive specimens, 43.9% (594) were monomicrobial, while 56.1% (758) were polymicrobial. The odds of resistance to ampicillin (p=0.005), amoxicillin/clavulanate (p=0.008), five different cephalosporins, vancomycin (p=<0.0001), and tetracycline (p=0.010) increased with each additional species present in a polymicrobial specimen. In contrast, the odds of resistance to piperacillin/tazobactam decreased by 75% for each additional species present (95% confidence interval [CI], 0.61-0.94; p=0.010). For one or more antibiotics tested, 13 pairs of bacterial species exhibited statistically significant interactions compared with the expected resistance rate obtained with the Highest Single Agent Principle and Union Principle (Vollstedt, 2020).

Haley (2023) reported the results of a prospective non-randomized controlled trial involving 577 adults with recurrent UTIs with treatment guided by either M-PRC/P-AST (Guidance UTI test, n=252) or standard urine culture (n=146). Selection of study group was at the treating clinicians' preference, as was the choice of treatment plan. Experimental and control group participants were matched for age, sex, and baseline symptom scores for the analysis. A study questionnaire was self-administered by the study participants on day 1, from day 2 through day 14, and a follow-up survey on day 30. Treating clinicians completed a treatment decision survey. The turn-around time for results, from sample receipt by the lab to the return of results, were reported. The results indicated M-PCR/P-AST results were returned significantly faster, with a mean of 1.45 days for the M-PCR/P-AST group vs. 2.87 days for the control group (p<0.0001). The authors created a composite measure of three negative outcomes; 1) recurrence of UTI symptoms, 2) visits to a medical provider for UTIs, and 3) visits to urgent care, emergency department, or hospital stays for UTIs. The M-PCR/P-AST group was found to have significantly fewer negative outcomes in composite scores vs. the control group (p=0.018). The control group had more UTI-related visits to medical providers, visits to urgent care and emergency department, or hospitalizations vs. the M-PCR/P-AST group (p=0.01 and p=0.45, respectively). There were no statistically significant differences in the recurrence of UTI symptoms between the two groups (p=0.26). Among participants of all ages, there was no significant difference between groups with regard to the percent of participants treated with antimicrobial agents (p=0.55). The utility of the results of this study are limited by several factors, including lack of randomization and blinding, lack of standardization in treatment protocols, and other significant factors.

Korman (2023) published the interim results of an observational prospective study involving 264 participants with complicated UTIs and positive M-PCR/P-AST results. Participants were stratified by those who were treated or not treated with antimicrobials, including antibiotic and anti-fungal drugs through 14 days. Study results were based on the self-reported American English Acute Cystitis Symptom Score (ACSS) Questionnaire tool. The authors reported that 55.4% of participants had exclusively non-*E. coli* infections (n=115 treated vs. 31 untreated) and 72% had polymicrobial infections (n=162 treated vs. 28 untreated). The treated participants exhibited greater symptom reduction vs. untreated participants on day 14 for those with both exclusively non-*E. coli* organisms (p=0.006) and polymicrobial infections (p=0.002). Similarly, a higher percentage of treated participants achieved clinical cure for polymicrobial infections on day 14 (p=0.049). The results of this trial are unsurprising, as it would be expected that treated participants would have better outcomes than those who received no treatment for an infection. Additionally, the study design is of questionable utility, as it does not involve the comparison of participants treated with M-PCR/P-AST vs. those treated with standard care, which is the question of primary interest when assessing the clinical utility of a diagnostic test indicated for clinical management. Additionally, the unblinded methodology and lack of objective measures limits the value of the results.

In 2022 the American Urological Association (AUA), Canadian Urological Association (CUA), and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) published a new guideline addressing recurrent uncomplicated urinary tract infections in women (Anger, 2022). This document does not mention the use of combined pathogen identification and drug resistance testing in that population.

Other Conditions

In addition to UTIs, combined pathogen identification and drug resistance testing has been proposed as a diagnostic tool for additional conditions, including chronic wounds and respiratory, blood-borne, and gastrointestinal infections. Several studies are available that describe the use of the GenMark Dx® ePlex® test (Roche Diagnostics Corp, Indianapolis, IN) in the treatment of bacteremia. The GenMark Dx ePlex identifies 56 bacteria and fungi and 10 anti-infective agent resistance genes using combined pathogen identification and drug resistance testing.

Bryant (2020) reported on a study involving the retrospective testing of 187 blood samples of individuals being treated for sepsis. The panel identified all pathogens in 164 samples (87.7%) and did not identify 7% of pathogens. The sensitivity of the test was reported to be 100% for Gram-positive pathogens, 96% for Gram-negative pathogens and 88% in polymicrobial samples. The authors proposed that, in retrospective analysis using medical records from the sample donors, 45% would have had treatment modifications. Whether or not these findings reflect prospective treatment was not investigated.

Additional studies by Carroll (2020) and McCarty (2022) also reported on the possible impact of using combined pathogen identification and drug resistance testing with GenMark Dx ePlex testing using retrospective study methodologies in individuals with bacteremia compared to standard testing procedures. While these studies identify potential benefit to combined pathogen identification and drug resistance testing, data from well-designed and conducted prospective studies would be helpful in elucidating the clinical utility of such testing.

Conclusions

At this time the evidence addressing the use of combined pathogen identification and drug resistance testing is insufficient to demonstrate clinical utility. Whether or not improved clinical outcomes result from treatment guided by this testing method is unclear. Furthermore, it should be noted that the use of such tests pose a potential risk related to false positive results, treatment of unproblematic or benign conditions (over diagnosis), use of unnecessary follow-up tests and procedures, among other issues.

Adequate data from well-designed and conducted studies is needed elucidate these issues before the use of combined pathogen identification and drug resistance tests become accepted practice.

Background/Overview

Polymerase chain reaction (PCR) testing provides simplified DNA (deoxyribonucleic) analysis by amplification of the targeted gene or DNA sequence. One important prerequisite of PCR is that the sequence of the gene, or at least the borders of the region of DNA to be amplified, must be known. PCR testing may be useful when a culture is difficult due to the low numbers of organisms present in the specimen, for fastidious or lengthy culture requirements, or when there is difficulty in collecting an appropriate sample. Quantification of viral load via PCR has been used as a prognostic indicator and for follow/up of individual response to therapy. To date, PCR amplification techniques have been limited by challenges in the interpretation of test results, potential for false positive results and other confounders including specificities, sensitivities, and positive and negative predictive values for many microorganisms in sufficiently large population groups.

Since 1978, the FDA has approved several urine culture kits and devices (FDA, 2018), and multiple laboratories have developed specific urine culture tests that they must validate and perform in-house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA, '88). Several manufacturers have also developed PCR assays designed to detect multiple pathogens, such as the INFINITI® bacterial vaginosis QUAD assay, designed to detect bacteroides fragilis, gardnerella vaginalis, mobiluncus mulieris, mobiluncus curtisii, atopobium vaginae and prevotella bivia (AutoGenomics, Bacterial Vaginosis, 2010). The INFINITI candida vaginitis QUAD assay is designed to detect 5 fungal species: C. albicans, C. glabrata, C. krusei, C. parapsilosis, and C. tropicalis (AutoGenomics Candida Vaginitis 2010). Quest Diagnostics has developed the Quest SureSwab, which includes tests for C. trachomatis, N. gonorrhoeae, and T. vaginalis as well as tests for bacterial vaginosis and Candida spp.

As noted above, several technologically advanced tests for the identification of pathogens as well as their susceptibility to certain pharmacological treatments have become available. Such tests provide the potential for improved identification and treatment options to clinicians for a variety of infections, but as of yet have not been adequately studied to determine their impact on health-related outcomes.

Definitions

Antibiotic resistance testing, (also known as antimicrobial susceptibility testing): Refers to testing for the purpose of isolating causative microorganisms and guiding treatment decisions regarding antibiotic selection. Testing can be done by conventional methods (phenotypic testing) and newer molecular (genotypic) techniques such as PCR, NAAT and NGS.

Antimicrobial: An agent that kills microorganisms or stops their growth.

Genotypic: The genetic makeup of an organism or group of organisms with reference to a single trait, set of traits or an entire complex of traits.

Molecular testing: Relating to the study of molecules, a group of atoms bonded together, representing the smallest fundamental unit of a chemical compound that can take part in a chemical reaction.

Nucleic acid amplification test (NAAT or NAT): A type of genetic test used for infectious disease. This technique makes numerous copies (amplification) of any genetic material from the microbes present in a sample so that it can be more easily detected. One type of NAAT is polymerase chain reaction (PCR).

Phenotypic: Relating to the observable characteristics of an individual resulting from the interaction of its genotype with the environment.

Polymerase Chain Reaction (PCR): A laboratory technique used to make multiple copies of a segment of DNA.

Urinary Tract Infection (UTI): Refers to an infection of any part of the urinary system (kidneys, ureters, bladder, urethra).

Classifications of urinary tract infections (UTIs) (Bonkat, EAU, 2020):

> Uncomplicated UTIs: Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.
>
> Complicated UTIs: All UTIs which are not defined as uncomplicated. Meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e., all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases for example, diabetes.
>
> Recurrent UTIs: Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes. or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
87999	Unlisted microbiology procedure [when specified as a pooled antibiotic sensitivity test with multiplex PCR, such as the Guidance® UTI test]

0141U	Infectious disease (bacteria and fungi), gram-positive organism identification and drug resistance element detection, DNA (20 gram-positive bacterial targets, 4 resistance genes, 1 pan gram-negative bacterial target, 1 pan Candida target), blood culture, amplified probe technique, each target reported as detected or not detected ePlex® BCID Gram-Positive Panel, GenMark Diagnostics, Inc, GenMark Diagnostics, Inc
0142U	Infectious disease (bacteria and fungi), gram-negative bacterial identification and drug resistance element detection, DNA (21 gram-negative bacterial targets, 6 resistance genes, 1 pan gram-positive bacterial target, 1 pan Candida target), amplified probe technique, each target reported as detected or not detected ePlex® BCID Gram-Negative Panel, GenMark Diagnostics, Inc, GenMark Diagnostics, Inc
0321U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 20 bacterial and fungal organisms and identification of 16 associated antibiotic-resistance genes, multiplex amplified probe technique Bridge Urinary Tract Infection Detection and Resistance Test, Bridge Diagnostics
0369U	Infectious agent detection by nucleic acid (DNA and RNA), gastrointestinal pathogens, 31 bacterial, viral, and parasitic organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique GI assay (Gastrointestinal Pathogen with ABR), Lab Genomics LLC, Thermo Fisher Scientific
0370U	Infectious agent detection by nucleic acid (DNA and RNA), surgical wound pathogens, 34 microorganisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, wound swab Lesion Infection (Wound), Lab Genomics LLC, Thermo Fisher Scientific
0372U	Infectious disease (genitourinary pathogens), antibiotic-resistance gene detection, multiplex amplified probe technique, urine, reported as an antimicrobial stewardship risk score Qlear UTI - Reflex ABR, Lifescan Labs of Illinois, Thermo Fisher Scientific
0373U	Infectious agent detection by nucleic acid (DNA and RNA), respiratory tract infection, 17 bacteria, 8 fungus, 13 virus, and 16 antibiotic-resistance genes, multiplex amplified probe technique, upper or lower respiratory specimen Respiratory Pathogen with ABR (RPX), Lab Genomics LLC, Thermo Fisher Scientific
0374U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 21 bacterial and fungal organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, urine Urogenital Pathogen with Rx Panel (UPX), Lab Genomics LLC, Thermo Fisher Scientific

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

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6. Korman HJ, Mathur M, Luke N, et al. Multiplex polymerase chain reaction/pooled antibiotic susceptibility testing was not associated with increased antibiotic resistance in management of complicated urinary tract infections. Infect Drug Resist. 2023; 16:2841-2848.
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9. Vollstedt A, Baunoch D, Wolfe A, et al. Bacterial interactions as detected by pooled antibiotic susceptibility testing (P-AST) in polymicrobial urine specimens. J Surg Urol. 2020:1(1):1-10.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Anger J, Lee U, Ackerman AL, et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU Guideline (2022). Available at: https://www.auanet.org/guidelines-and-quality/guidelines/recurrent-uti. Accessed on February 15, 2024 .
2. Bonkat G, Pickard R, Bartoletti R, et al. European Association of Urology (EAU) Urological Infections Guidelines. 2023. Available at: http://uroweb.org/guideline/urological-infections/#3. Accessed on February 15, 2024.
3. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011; 52(5):e103-120.
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Websites for Additional Information

1. American Urological Association (AUA). Guideline: Catheter-Associated Urinary Tract Infections: Definitions and Significance in the Urologic Patient. 2014. Available at: https://www.auanet.org/guidelines-and-quality/quality-and-measurement/quality-

improvement/clinical-consensus-statement-and-quality-improvement-issue-brief-(ccs-and-qiib)/catheter-associated-urinary-tract-infections. Accessed on February 15, 2024.

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Qlear UTI
Respiratory Pathogen with ABR (RPX)
Urogenital Pathogen with Rx Panel (UPX)

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	02/15/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised document title. Revised position statement to address “combined pathogen identification and drug resistance” testing. Revised Description, Rationale, Background, References, Websites, and Index sections. Updated Coding section; added 0141U, 0142U, 0321U, 0369U, 0370U, 0373U and removed 81479 NOC (not applicable).
Reviewed	02/16/2023	MPTAC review. Updated Rationale and References sections. Updated Coding section with 04/01/2023 CPT changes; added 0372U, 0374U.
Reviewed	02/17/2022	MPTAC review. The Definitions and References sections were updated.
New	02/11/2021	MPTAC review. Initial document development.
