Executive summary and publications:

The Future of UTI Management From Tradition to Precision

A Multi-Dimensional, Prospective Research Trial (NCT06996301)

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Executive Summary: The DocLab UTM Clinical Research Program

For decades, the standard of care for diagnosing urinary tract infections has relied on conventional urine culture and sensitivity (C&S) testing. However, the management of complicated urinary tract infections (cUTIs) has increasingly exposed the limitations of this legacy approach. Prolonged turnaround times and the frequent failure to identify fastidious or polymicrobial pathogens routinely delay the initiation of targeted therapy, exacerbating patient morbidity and fueling antimicrobial resistance.

The **DocLab UTM Research Program**, anchored by the landmark multicenter randomized clinical trial NCT06996301, represents a definitive turning point in urological and infectious disease diagnostics. Enrolling 773 symptomatic adult patients across six U.S. sites, this rigorous, investigator-blinded study utilized a dual-testing methodology: both PCR and C&S were performed for all patients, while treating clinicians were randomized to act on only one set of results.

This comprehensive booklet compiles eight pivotal publications, comprising six distinct analyses of the clinical trial (Parts I–VI), a systematic review, and an expert commentary, that collectively establish the clinical validity, utility, and economic superiority of PCR-guided cUTI management.

Key Pillars of Evidence

1. Superior Clinical Outcomes and Rapid Turnaround (Part I & Part VI) The primary objective of diagnostic testing is to improve patient care. The data unequivocally demonstrate that therapeutic management guided by PCR yields significantly better clinical outcomes compared to C&S (88.08% favorable outcomes vs. 78.11%). This success is largely driven by a dramatic reduction in diagnostic turnaround time, averaging 49.68 hours for PCR versus 104.4 hours for C&S. Advanced mediation analysis revealed that this accelerated speed to actionable data directly facilitated earlier antibiotic initiation (median 20 hours vs. 52 hours), which accounted for the vast majority of improved symptom resolution.

2. Unmasking the True Infection Landscape (Part II & Part III) cUTIs are notoriously complex, yet C&S frequently underestimates their polymicrobial nature. PCR accurately identified polymicrobial infections in 43.52% of cases, compared to only 31.95% by C&S. The clinical consequences of these missed pathogens are severe: when C&S failed to detect polymicrobial infections or phenotypic resistance present in the PCR analysis, patient clinical failure rates spiked to 33.33% and 50%, respectively. Furthermore, analyzing discordant results revealed that patients treated for PCR-positive but C&S-negative infections achieved a 77.45% favorable clinical outcome, proving that PCR identifies true, actionable infections rather than false positives.

3. Precision Antimicrobial Stewardship (Part V) Antimicrobial resistance (AMR) is a global crisis. The research program confirms high genotype-phenotype concordance, meaning the rapid detection of AMR genes via multiplex PCR reliably predicts actual phenotypic resistance. By providing this data days ahead of conventional C&S, PCR empowered clinicians to select more appropriate, targeted antibiotics, often leading to successful oral medication regimens rather than escalating to intravenous or intramuscular broad-spectrum alternatives.

4. Analytical Validity and Pre-Analytic Robustness (Part IV) Bridging the gap between molecular signals and viable bacterial burden, the program validated the use of semi-quantitative ΔCt thresholds. The analysis proved that conventional C&S is highly vulnerable to processing delays, which lead to time-dependent bacterial viability loss. PCR bypasses these pre-analytic vulnerabilities, ensuring accurate diagnostics regardless of transit times.

Real-World Impact and the Future of cUTI Care

Beyond the clinical trial, the compiled **Systematic Review** and **Expert Commentary** validate the alignment of PCR-based diagnostics with stringent MolDX Medicare coverage criteria. Real-world evidence confirms that the integration of comprehensive PCR panels reduces long-term healthcare costs, minimizes empirical antibiotic misuse, and decreases UTI recurrence and hospital readmissions.

The Conclusion is Clear: The integration of PCR testing into the standard management of cUTI is no longer just an alternative; it is a clinical necessity. This research program provides the foundational evidence required to support a paradigm shift toward a dual-testing model (PCR + C&S), elevating the standard of care from empirical guesswork to definitive, precision medicine.

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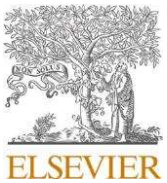

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Clinical utility of PCR compared to conventional culture and sensitivity testing for the management of complicated urinary tract infections in adults: Part I. Assessment of clinical outcomes, investigator satisfaction scores, and turnaround times

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Keywords:
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ABSTRACT

Purpose: Managing complicated urinary tract infections (cUTIs) poses significant challenges, often resulting in the overprescription of empiric antibiotics. This approach exposes patients to multiple antimicrobials and raises the risk of inadequate treatment efficacy. The purpose of this study is to assess and compare the clinical utility of molecular testing (PCR) versus conventional culture and sensitivity (C&S) in managing cUTI, to identify optimal management strategies for cUTI patients.

Materials and methods: 773 symptomatic adult patients with suspected cUTI diagnosis were randomized (1:1) into either the PCR-guided treatment group or the control group (C&S-guided) and followed up for 28 days. The primary outcome measure was the number (and percentage) of patients in each study arm with favorable clinical outcomes at the end of the study visit.

Results: Overall, 468 patients completed all study procedures, and of those, data from 362 patients were analyzed (193 PCR arm, 169 C&S arm) for this Part 1 of the primary study analysis. Treatments guided by PCR results provided significantly better clinical outcomes compared to treatments guided by conventional C&S results (88.08 % vs. 78.11, $p = 0.011$), with a significantly shorter mean turnaround time (49.68 h vs. 104.4 h, $p < 0.001$), and a significant higher investigator satisfaction total score (23.95 ± 1.96 vs. 20.64 ± 4.12, $p < 0.001$).

Conclusions: This data demonstrated the clinical utility of PCR in improving therapeutic clinical outcomes and facilitating expedited, patient-specific management of cUTI for optimal patient care. Furthermore, this study showed a clear preference among investigators for PCR over C&S when making clinical decisions and managing patients with cUTI.

URINARY tract infections (UTIs) are among the most common reasons for a patient to visit a clinic and are the second most common type of bacterial infection in adults [1]. Up to 33 % of all women experience a UTI in their lifetime. While a well-studied list of microorganisms is commonly associated with UTIs, a broader range of microorganisms may be involved, and polymicrobial infection often complicates the

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Clinical utility of PCR compared to conventional culture and sensitivity testing for management of complicated urinary tract infections in adults: Part II. Evaluation of diagnostic concordance, discordant results, and antimicrobial selection efficacy

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Keywords:
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ABSTRACT

Purpose: Complicated urinary tract infections (cUTIs) are difficult to manage due to their polymicrobial nature and resistance to standard therapies. In current clinical practice, the management of a cUTI often starts with broad-spectrum antimicrobials until culture and sensitivity (C&S) results are available, but these diagnostic delays further hinder treatment efficacy. Polymerase Chain Reaction (PCR) offers a faster alternative. This study evaluates PCR's utility compared to C&S, focusing on agreeability, discordant results, clinical outcomes, and antimicrobial selection efficacy to improve cUTI management.

Materials and Methods: The clinical study was conducted in two parts: the primary study focused on patients with cUTIs, while the sub-study involved healthy individuals without signs or symptoms of urinary tract infection (UTI). All collected samples underwent analysis using both PCR and C&S for comparison. Building on the first part of the study, the research evaluated outcome measures related to discordant analysis.

Results: Overall, our study supports good agreement between PCR and C&S in positive cases (95.32 % at baseline and 88.06 % at end of study (EOS)) but reveals some discordance in negative cases (38.30 % at baseline and 62.91 % at EOS). The negative percent agreement (NPA) in the sub-study on the healthy population was 70.16 %. Further analysis of discordant results revealed that symptomatic patients treated for PCR-positive infections trended toward better clinical outcomes (77.45 % vs. 71.42 %) and higher rates of microbiological eradication (53.92 % vs. 50 %) compared to those treated for C&S-positive infections. Additional analysis on antimicrobial use and microbiological aspects revealed that the PCR group received more oral medication-based treatments, while the C&S group received other forms (intramuscular or bladder irrigation). In cases of discordant results, there were more PCR-positive but culture-negative cases than PCR-negative but culture-positive cases.

Conclusions: Our clinical utility study data suggests that PCR-guided management of cUTIs is overall superior to conventional C&S, offering several advantages. PCR has the potential to enhance patient care by enabling the early adoption of narrower antibiotic therapies, improving clinical outcomes, and ensuring the effective selection of antimicrobials. A PCR-guided management plan could be particularly beneficial in managing patients with cUTIs, addressing infections that are occasionally overlooked with current C&S-guided treatment protocols.

Abbreviations: CFU, Colony-forming unites; C&S, Culture and sensitivity; cUTI, Complicated urinary tract infection; EOS, End of study; FCl, Favorable clinical outcome; ITT, Intention-to-treat; Mod-ITT, Modified intention-to-treat; NPA, Negative percent agreement; PCR, Polymerase chain reaction; PPA, Positive percent agreement; UTI, urinary tract infection; V1, Visit 1; V3, Visit 3.

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Article

The Clinical Validity and Utility of PCR Compared to Conventional Culture and Sensitivity Testing for the Management of Complicated Urinary Tract Infections in Adults (Part III): A Secondary (Ad Hoc) Analysis of Pathogen Detection, Resistance Profiles, and Impact on Clinical Outcomes

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Abstract: Clinical success in treating complicated urinary tract infections (cUTIs) depends on accurate pathogen detection, given the common occurrence of polymicrobial infections and antimicrobial resistance. This multicenter, randomized, investigator-blinded study compared polymerase chain reaction (PCR)-based diagnostics to conventional culture and sensitivity (C&S) testing in guiding the treatment of cUTIs. PCR identified polymicrobial infections in 43.52% of cases, a significantly higher rate than that observed with C&S (31.95%, $p = 0.033$). Patients in the C&S arms with undetected polymicrobial infections had a significantly higher clinical failure rate (33.33%, 14/42, $p = 0.041$) compared to those with concordant polymicrobial infection identification by both methods (22.22%, 12/54). PCR also detected additional pathogens in 54.44% (92/169) of cases in the C&S arm, where clinical failure was significantly higher when C&S missed pathogens (28.26% vs. 14.29%, $p = 0.015$). Similarly, when C&S failed to detect phenotypic resistance (compared to PCR), clinical failure occurred in 50% (16/42) of cases, compared to 13.22% (21/121, $p = 0.001$) when resistance detection was concordant (PCR and C&S). To further illustrate the clinical impact, patient-level case analyses are included to demonstrate how PCR-guided therapy improved pathogen detection and enabled more appropriate antimicrobial selection compared to C&S. These findings highlight the limitations of C&S in detecting polymicrobial infections, antimicrobial resistance, and hetero-resistance due to its limited clonal analysis, supporting the integration of PCR for more accurate diagnostics and optimized cUTI management.

Keywords: urinary tract infection; polymerase chain reaction; microbial sensitivity tests; antimicrobial drug resistance; polymicrobial infections; molecular diagnostic testing; patient-relevant outcome

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1. Introduction

Complicated urinary tract infections (cUTIs) present a significant clinical challenge due to their complex microbial etiology, rising antimicrobial resistance, and potential for

diagnostics

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Semi-Quantitative ΔCt Thresholds for Bacteriuria and Pre-Analytic Drivers of PCR-Culture Discordance in Complicated UTI: An Analysis of NCT06996301 (Part IV)

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Abstract

Background: Quantitative urine culture (CFU/mL) remains the reference standard for diagnosing urinary tract infections (UTIs) but is limited by delayed turnaround times and sensitivity to pre-analytic factors. Multiplex PCR panels offer rapid detection; however, standardized mappings between molecular signals and viable bacterial burdens are insufficiently defined. We used the multicenter NCT06996301 paired dataset to evaluate the analytical validity (AV), clinical validity (CV), and pre-analytic robustness of ΔCt (Ct_target − IC_Ct) as a semi-quantitative indicator of bacterial load. **Methods**: We analyzed 1027 paired PCR and quantitative urine culture specimens from six sites. The primary molecular predictor was ΔCt (Ct_target − IC_Ct). Species-level Spearman and Pearson correlations, species-specific linear mixed-effects calibration models ($\log_{10}$CFU ~ ΔCt + (1|site)), and ROC analyses were performed for the taxa meeting pre-specified sample thresholds. A pooled multilevel model assessed the collection method and time-to-processing (hours) effects ($\log_{10}$CFU ~ ΔCt × collection_method + ΔCt × time_to_processing_h + (1|site) + (1|run)). AV was assessed via reproducibility, internal control normalization, and site run variance. CV was assessed by ΔCt calibration and discrimination. Clinical utility (CU) was contextualized using outcomes from the parent randomized trial. **Results**: PCR positivity exceeded culture positivity across all sites (PCR ~82–88% vs. culture ~66–70%); this excess likely reflects a combination of molecular detection of non-viable DNA, detection of fastidious taxa less readily recovered by culture, and pre-analytic effects. For six common uropathogens (n = 90 pairs/species), ΔCt correlated strongly with $\log_{10}$CFU (Spearman ρ = −0.64 to −0.75; Pearson r = −0.75 to −0.83). Species-specific mixed models yielded slopes of −0.746 to −0.922 $\log_{10}$CFU per ΔCt unit (all $p < 0.001$), indicating that each 1 unit ΔCt change corresponds to a ~5.6–8.4-fold CFU difference. ROC AUCs for ΔCt discrimination were 0.78–0.84 (interpreted as good discrimination, i.e., ΔCt meaningfully improves the clinician's probability estimate of a high CFU but does not perfectly classify every specimen). The collection method (catheter vs. clean-catch) did not materially modify the ΔCt→CFU relationship, whereas the processing delay was associated with reduced recovered CFU (~0.048 $\log_{10}$CFU lost per hour) and a significant ΔCt × time interaction, consistent with time-dependent viability loss driving the PCR$^+$/culture$^-$ discordance. **Conclusions**: ΔCt from the DOC Lab UTM 2.0 panel shows a reproducible, analytically valid semi-quantitative measure of urinary bacterial load. Laboratories can derive assay- and workflow-specific ΔCt cut points for semi-quantitative reporting, but thresholds must be validated prospectively and paired with operational controls for specimen handling.

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Article

Genotype–Phenotype Concordance and Ct-Informed Predictive Rules for Antimicrobial Resistance in Adult Patients with Complicated Urinary Tract Infections (Part V): Clinical and Stewardship Implications from the NCT06996301 Trial

Moustafa Kardjadj [1,*], Itoe P. Priestly [2], Roel Chavez [3], DeAndre Derrick [3] and Thomas K. Huard [4]

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Abstract

Background: Rapid molecular detection of antimicrobial resistance (AMR) can shorten time to effective therapy in complicated urinary tract infections (cUTI), but the ability of gene presence and quantitative PCR signal (Ct, and ΔCt = Ct_marker − IC_Ct) to predict phenotypic non-susceptibility and clinical outcomes requires rigorous evaluation. We analyzed marker-level concordance, Ct→MIC relationships, and the clinical impact pathway in the randomized NCT06996301 trial. **Methods**: Marker–phenotype concordance metrics (sensitivity, specificity, PPV, NPV, LR+, LR−, κ) were computed for selected marker × species strata with stable sample sizes. Mixed-effects models ($\log_2$[MIC] ~ ΔCt_marker + IC_Ct + collection_method + prior_abx + (1|site)) assessed quantitative Ct→MIC associations. ROC analyses evaluated ΔCt discrimination of phenotypic non-susceptibility. A pre-specified sensitivity analysis included smaller strata ($n \leq 20$) with bootstrap 95% confidence intervals for ΔCt slopes and AUCs. Clinical analyses compared PCR-guided ($n = 193$) versus culture-guided ($n = 169$) arms for time-to-antibiotic and treatment success using adjusted logistic regression and causal mediation (time-to-antibiotic as mediator; bootstrap inference). **Results**: High genotype–phenotype concordance was observed for canonical markers (e.g., $bla_{\text{CTX-M}}$ in *E. coli*: sensitivity 0.94 [95% CI 0.88–0.97], specificity 0.995 [95% CI 0.990–0.998], κ ≈ 0.93). Mixed models showed modest but significant Ct→MIC associations for select markers (e.g., $bla_{\text{CTX-M}}$ in *E. coli*: ΔCt slope −0.15 [95% CI −0.27 to −0.02], $p = 0.015$). The sensitivity analysis ($n \leq 20$ strata) confirmed consistent negative directions, with robust bootstrap CIs excluding zero for *qnrS* (*E. coli*), *tetM* (*E. coli*), *blaNDM* (*Klebsiella*), and *qnrS* (*Proteus*). ROC AUCs for ΔCt prediction of non-susceptibility ranged from 0.62 to 0.81 (95% CIs ≈ 0.47–0.97). Clinically, PCR guidance shortened median time to antibiotic initiation (20 h vs. 52 h) and increased treatment success (88.1% vs. 78.1%; adjusted OR 1.95 [95% CI 1.12–3.40], $p = 0.018$). Mediation analysis estimated that 63% (ACME 0.112 [95% CI 0.045–0.178], $p = 0.002$) of the treatment success benefit was mediated through earlier antibiotic initiation. **Conclusions**: Binary detection of high-impact AMR genes by multiplex PCR reliably predicts phenotypic non-susceptibility and accelerates effective therapy when integrated with stewardship workflows. Quantitative PCR (ΔCt) provides modest but reproducible information about MIC magnitude and may flag heteroresistant subpopulations. A pragmatic implementation model combining rapid PCR with conventional culture is recommended to optimize clinical benefit while retaining isolate recovery for definitive AST.

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Article

Clinical Symptom Resolution Following PCR-Guided vs. Culture and Susceptibility-Guided Management of Complicated UTI (Part VI): How Time-To-Antibiotic Start and Antibiotic Appropriateness Mediate the Benefit of Multiplex PCR—An Ad Hoc Analysis of NCT06996301

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Abstract

Background: Rapid multiplex PCR assays promise faster and broader detection of uropathogens and resistance markers than conventional quantitative urine culture and susceptibility testing (C&S), but trial evidence linking PCR-guided management to patient- centered outcomes and the mechanisms of any benefit is limited. We performed an ad hoc analysis of the randomized, multicenter NCT06996301 trial to evaluate whether PCR- guided diagnostic management improves clinical symptom resolution in complicated urinary tract infection (cUTI) and to quantify mediation by time-to-antibiotic start and an- tibiotic appropriateness. **Methods:** Paired PCR and C&S were collected for all participants; treating investigators received and acted on randomized results from one diagnostic modal- ity and remained blinded to the comparator. The modified intention-to-treat (Mod-ITT) cohort at end-of-study (EOS) included 362 participants (PCR n = 193; C&S n = 169). The primary outcome was complete clinical cure at EOS (absence of all baseline symptoms). Secondary outcomes included partial cure (≥50% symptom reduction) and per-symptom changes. We used mixed-effects logistic regression (site random intercept) to estimate associations, and causal mediation analysis with nonparametric bootstrap (B = 2000) to decompose PCR's total effect into indirect effects via time-to-antibiotic (log-transformed) and antibiotic appropriateness (binary, adjudicated at EOS) for complete clinical cure and partial cure. **Results:** Median time-to-first antibiotic was substantially shorter in the PCR arm (20 h; IQR 12–36) than in the C&S arm (52 h; IQR 30–66; $p < 0.001$). Antibiotic appropriateness was higher after PCR-guided care (161/193; 83.4%) versus C&S (105/169; 62.1%; $p < 0.001$). Complete clinical cure occurred in 143/193 (74.1%) PCR versus 106/169 (62.7%) C&S ($p = 0.020$); partial cure in 161/193 (83.4%) versus 121/169 (71.6%; $p = 0.014$). In a total-effect mixed model (no mediators), PCR assignment was associated with higher odds of cure (adjusted OR 1.95; 95% CI 1.12–3.39; $p = 0.018$). In the mechanistic model including mediators, antibiotic appropriateness (OR 2.48; 95% CI 1.45–4.24; $p = 0.001$), and time-to-antibiotic (per 1 h, OR 0.95; 95% CI 0.926–0.975; $p < 0.001$) were independently predictive, while the direct arm effect was attenuated (OR 1.10; 95% CI 0.33–3.71). Me- diation analysis estimated a statistically significant combined indirect effect (ACME) of 0.0648 (95% CI 0.0343–0.0977), ADE 0.0207 (95% CI −0.0282–0.0784), total effect 0.0796 (95% CI 0.0419–0.1225), and proportion mediated ≈ 74%. Both time-to-antibiotic and appropriateness contributed, with ACME_time ≈ 0.046 and ACME_appropriateness ≈ 0.019. Exploratory analysis using partial cure as the outcome confirmed the robustness and in- ternal validity of the complete-cure findings. **Conclusions**: In this ad hoc analysis of a randomized trial, PCR-guided management of cUTI improved patient-centered symptom outcomes compared with culture-guided care. Most of the benefit was mediated through faster initiation of antibiotics and, to a lesser extent, increased probability of an appropriate initial antibiotic. These results support stewardship-integrated, rapid molecular diagnostics (used alongside culture) to shorten time-to-effective therapy and improve clinical outcomes in cUTI.

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REVIEWS IN UROLOGY

Evaluating the Analytical Validity and Clinical Utility and Validity of Polymerase Chain Reaction Diagnostics vs Culture and Sensitivity Methods in Complicated Urinary Tract Infection Management

A Comprehensive Review of Real-World Evidence, Clinical Trials, and Meta-Analyses Concerning Molecular Diagnostic Services Program Coverage Criteria

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KEYWORDS:
Polymerase chain reaction; microbial sensitivity tests; urinary tract infections; validation study; insurance, health, reimbursement

Abstract

Background: Polymerase chain reaction (PCR)–based diagnostics are increasingly used for complicated urinary tract infections, offering faster and more sensitive detection of pathogens than conventional culture and sensitivity methods. This review assessed the clinical validity, utility, and alignment of PCR-based diagnostics with the Molecular Diagnostic Services Program's (MolDX) Medicare coverage and reimbursement criteria.

Methods: A systematic evaluation of real-world evidence, clinical trials, systematic reviews, and meta-analyses was conducted to compare the diagnostic accuracy, turnaround times, and clinical impact of PCR-based testing with traditional culture methods. Studies assessing sensitivity, specificity, and cost-effectiveness were included.

Results: Findings demonstrate that PCR-based diagnostics substantially enhance diagnostic accuracy and reduce time to pathogen identification. Clinical studies indicate that PCR-based methods improve patient outcomes by expediting appropriate antimicrobial therapy, reducing symptom duration, decreasing complications, and shortening hospital stays. In addition, clinical utility studies highlight cost savings and reduced reliance on empirical antibiotic use, contributing to antimicrobial stewardship.

Conclusion: Use of PCR-based diagnostics for complicated urinary tract infections offers substantial advantages over conventional methods, improving diagnostic efficiency, clinical outcomes, and cost-effectiveness. Evidence supports their alignment with MolDX reimbursement criteria, advocating for broader adoption and Medicare coverage of PCR as a robust, cost-effective diagnostic tool in modern health care.

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Commentary

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Clinical Utility of PCR in Complicated Urinary Tract Infections: A Paradigm Shift in Diagnostics and Management

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In the realm of medical diagnostics, the evolution of technology often compels a re-evaluation of established practices. Just as the direct examination of a patient's urine for a "honey taste" to diagnose diabetes mellitus has been superseded by sophisticated scientific advances,[1] so too must the diagnostic approach to complicated urinary tract infections (cUTIs) evolve beyond the inherent limitations of conventional culture and sensitivity (C&S) testing. Complicated UTIs, defined as urinary tract infections occurring in the presence of host risk factors such as indwelling catheters, urolithiasis, diabetes mellitus, immunosuppression, or structural and functional urinary tract abnormalities, remain a formidable challenge, characterized by complex microbial etiologies, escalating antimicrobial resistance, and significant risks of morbidity and mortality.[2] The prolonged turnaround times (TAT) inherent in C&S often delay the initiation of effective, targeted therapy, leading to suboptimal patient outcomes and contributing to the broader crisis of antibiotic resistance. In this critical landscape, PCR-based diagnostics have emerged as a transformative solution, providing rapid and comprehensive pathogen identification, as well as resistance gene detection. The robust evidence from the US multicenter randomized trial (NCT06996301) provides compelling support for a paradigm shift in cUTI management, necessitating a reevaluation of current diagnostic and therapeutic approaches.

THE FOUNDATIONAL ADVANCE: INSIGHTS FROM THE NCT06996301 TRIAL

The NCT06996301 trial (Advarra IRB ID: Pro00071764), a large-scale, investigator-blinded, multicenter randomized study involving 773 adult cUTI patients across 6 US sites, directly compared PCR-guided management against conventional C&S testing.[3] A critical aspect of its robust design was the dual-testing approach: both PCR and C&S tests were performed for all patients at baseline and end of study (EOS), irrespective of their assigned treatment arm. Investigators, however, were blinded to the comparator test results, ensuring that treatment decisions were based solely on the randomly assigned diagnostic method. This meticulous design enabled an unparalleled side-by-side comparison of diagnostic accuracy, therapeutic guidance, and clinical outcomes, providing invaluable insight into the clinical utility of each method.[3]

The findings from the NCT06996301 trial, published in 3 parts, collectively underscore PCR's significant advantages over C&S across multiple critical domains, challenging the traditional reliance on slower, less comprehensive methods.

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Part I of the trial demonstrated that PCR-guided therapy led to significantly improved favorable clinical outcomes (defined as resolution of at least one symptom and absence of retreatment) in 88.08% of PCR patients compared with 78.11% of C&S patients ($P = .011$).[3] The overall microbial eradication efficiency was better among patients treated based on PCR results vs those treated based on C&S, however, without a statistically significant effect (62.18% vs 56.21%, $P = .24$). Substantial operational benefits complemented this clinical superiority; investigator satisfaction scores were markedly higher for PCR (mean 4.6/5) compared with C&S (3.8/5; $P < .001$), reflecting a more streamlined and effective diagnostic process. Furthermore, the mean diagnostic TAT was nearly halved with PCR (49.7 hours) vs C&S (104.4 hours; $P < .001$).[3] This rapid TAT is crucial, enabling earlier initiation of appropriate, targeted therapy, thereby minimizing patient morbidity, reducing the risk of complications, and optimizing healthcare resource utilization.

Part II of the study examined diagnostic concordance, reporting 88.1% sensitivity and 62.9% specificity at EOS. The lower specificity reflects PCR's ability to detect fastidious or polymicrobial infections that C&S misses, particularly in a symptomatic cUTI cohort with underlying risk factors, rather than false positives. Indeed, 174 PCR+/C&S– symptomatic cases at baseline achieved 77.45% favorable clinical outcomes, and 53.92% microbiological eradication, suggesting these represented true infections requiring treatment. Additional analysis on antimicrobial use and microbiological aspects revealed that the PCR group received more oral medication-based treatments, while the C&S group received other forms (intramuscular and even bladder irrigation).[4]

An ad hoc analysis (Part III) of the trial's data by Kardjadj et al[5] further evaluated pathogen detection, resistance profiling, and clinical outcomes. PCR detected polymicrobial infections in 43.52% of samples compared with 31.95% by C&S ($P = .033$). Patients in the C&S arms with undetected polymicrobial infections had a significantly higher clinical failure rate (33.33%, $P = .041$) compared with those with concordant polymicrobial infection identification by both methods (22.22%). PCR also detected additional pathogens in 54.44% of cases in the C&S arm, where clinical failure was significantly higher when C&S missed pathogens (28.26% vs 14.29%, $P = .015$). Similarly, when C&S failed to detect phenotypic resistance (compared with PCR), clinical failure occurred in 50% of cases, compared with 13.22% ($P = .001$) when resistance detection was concordant (PCR and C&S).

Beyond clinical efficacy, the economic and regulatory landscape strongly supports the adoption of PCR in cUTI management, presenting a compelling argument for its integration into standard practice. The trial's findings align seamlessly with the Molecular Diagnostic Services (MolDX) Program's coverage criteria, which mandate that expanded syndromic panels must demonstrably impact clinical management and improve patient outcomes.[6] A comprehensive review by Aberger et al[7] of 8 real-world evidence (RWE) studies demonstrates that broad panel PCR platforms consistently outperform culture alone, identifying fastidious and polymicrobial pathogens missed by routine methods, and enabling earlier, targeted therapy that reduces empirical antibiotic use and improves clinical outcomes. Moreover, Aberger et al[7] review confirms that the PCR panel (DocLab 2.0 UTM) used in NCT06996301 satisfies MolDX's stringent analytical and clinical validity criteria, achieving high accuracy, substantially shortening time to appropriate therapy, and delivering measurable gains in patient outcomes.

RWE from Ko et al[8] offers a compelling economic and clinical argument for integrating PCR into cUTI management. In a Medicare cohort of patients with complicated or recurrent UTIs, PCR-guided diagnostics reduced the incidence of recurrence from 72.0% to 65.2%, while cutting mean 1-year UTI-related costs from $1131 to $629 per patient, a statistically significant saving of $502 ($P = .004$). Moreover, nonoutpatient resource utilization (including hospitalizations and emergency visits) dropped from 53.4% in the culture group to 22.5% in the PCR cohort. These savings reflect PCR's ability to enable earlier, more targeted therapy, diminish broad spectrum antibiotic use, and avert costly complications and readmissions. Such multidimensional value (clinical, operational, and economic) is critical to adopting guidelines and payer support for PCR testing in cUTI care.

THE PATH FORWARD: IMPLICATIONS AND NEXT STEPS

The robust evidence from the NCT06996301 clinical trial and RWE studies marks a pivotal moment in cUTI diagnostics, demanding a re-evaluation of current practices and a clear roadmap for the future. The question is no longer *if* PCR is superior, but *how* we integrate this advanced diagnostic into the fabric of routine clinical care to maximize its transformative potential.

Clinical Practice Transformation

It is understood that adopting PCR panels system-wide presents logistical, billing, and training challenges. To facilitate practical implementation, a parallel combination of PCR and conventional C&S testing should be considered for patients with

cUTIs. Implementing this combined strategy represents a paradigm shift in cUTI management, moving from empiric, delayed therapy to precision medicine. Rapid PCR results empower clinicians to:

- *Initiate targeted therapy sooner:* By identifying pathogens and resistance genes within 24 to 48 hours, PCR performed in parallel with culture enables clinicians to initiate targeted, narrow-spectrum antibiotic therapy much earlier—often by day 1. Although culture continues to be processed to confirm or adjust therapy, the availability of rapid PCR results helps minimize delays and reduce treatment failures. This dual-testing approach supports faster recovery, better stewardship, and lowers the risk of resistance development.
- *Enhance antimicrobial stewardship:* The precise information provided by PCR in conjunction with phenotypic culture confirmation facilitates de-escalation of therapy, minimizes inappropriate antibiotic use, and helps preserve the efficacy of existing antimicrobial agents. This combined methodology is a critical step in combating multidrug resistance, especially in cUTI, where resistance rates are high and broad spectrum overuse is rampant.
- *Improve patient stratification and management:* Detecting polymicrobial infections and subtle resistance patterns through PCR while retaining culture for confirmation and phenotypic resistance surveillance allows for more nuanced, personalized treatment plans. This dual-modality approach reduces the likelihood of treatment failure and recurrent infections, ultimately improving patient outcomes and quality of life.

Future Research Directions

While NCT06996301 and other RWE studies provide a strong foundation, several critical questions warrant further investigation:

- *Utility in specific subgroups:* Further research should explore the optimal utility of PCR in specific patient populations, such as immunocompromised individuals and pediatric patients, where diagnostic challenges are particularly acute and the consequences of delayed or inappropriate treatment are severe.
- *Integration with advanced analytics:* Investigating the integration of PCR data and other molecular tools (sequencing) with artificial intelligence and machine learning algorithms could lead to predictive analytics for treatment response, resistance trends, and even personalized risk assessment for cUTI, moving beyond reactive diagnostics to proactive management.
- *Comparative effectiveness and cost-benefit in diverse settings:* While Ko et al[8] provided health economic RWE, further studies are needed to evaluate the cost-effectiveness and clinical benefits of PCR across diverse healthcare settings, including outpatient clinics, long-term care facilities, and acute care hospitals, to inform broader implementation strategies and ensure equitable access.

Policy and Implementation

For PCR to realize its full potential, concerted efforts are needed to address policy and implementation challenges, ensuring equitable access and seamless integration into healthcare systems:

- Guideline integration: Professional societies, including the AUA and Infectious Diseases Society of America, should consider reviewing and updating their cUTI management guidelines to include the parallel use of PCR and C&S testing as a unified diagnostic strategy, reflecting the latest evidence. This dual-testing recommendation would provide clear, evidence-based guidance for clinicians and standardize practice across institutions.
- *Overcoming implementation barriers:* Practical strategies should be developed to support cotesting workflows, including initial capital investment for laboratory infrastructure, cross-training laboratory personnel and clinicians on interpreting molecular and phenotypic results, and the integration of combined PCR and C&S data into electronic medical records to ensure efficient workflow and data utilization.
- *Payer engagement and innovative reimbursement models:* Continued engagement with payers is essential to ensure consistent and equitable reimbursement for PCR testing, recognizing that it has demonstrated clinical utility and cost-effectiveness. This involves developing new reimbursement models that account for the downstream savings generated by PCR, such as reduced hospitalizations and complications.

CONCLUSIONS

The robust evidence from the NCT06996301 trial and supporting real-world studies unequivocally supports the integration of PCR into cUTI care. This level of evidence parallels the standard required by the FDA to approve new therapies or recommend practice changes.

To mitigate the logistical, billing, and training challenges associated with systemwide PCR adoption, a combined approach, performing PCR in parallel with conventional C&S testing, offers a practical, evidence-based pathway to enhance diagnostic speed and accuracy while preserving the benefits of conventional methods (http://links.lww.com/JU9/A150).

This foundational advance, much like the evolution of diabetes diagnostics, deserves serious consideration by clinicians, guideline committees, and payers.

Embracing a dual-testing paradigm will pave the way for a more precise, efficient, and effective approach to combating complicated and recurrent urinary tract infections while safeguarding the future of antimicrobial efficacy.

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DATA AVAILABILITY
All data analyzed in this commentary are derived from published studies. The data sets used or analyzed during the current study are publicly available from the respective sources cited in the article. No original data were collected or generated specifically for this review.

AUTHOR CONTRIBUTIONS
Conceptualization: Kardjadj. Investigation: Kardjadj. Writing—review & editing: Kardjadj.

REFERENCES

1. Xu R, Deebel N, Casals R, Dutta R, Mirzazadeh M. A new gold rush: a review of current and developing diagnostic tools for urinary tract infections. *Diagnostics (Basel).* 2021;11(3):479.
2. Grey B, Upton M, Joshi LT. Urinary tract infections: a review of the current diagnostics landscape. *J Med Microbiol.* 2023;72(11):10.
3. Spangler FL, Williams C, Aberger ME, et al. Clinical utility of PCR compared to conventional culture and sensitivity testing for the management of complicated urinary tract infections in adults: part I—assessment of clinical outcomes, investigator satisfaction scores, and turnaround times. *Diagn Microbiol Infect Dis.* 2025;111(1):116601.
4. Spangler FL, Williams C, Aberger ME, et al. Clinical utility of PCR compared to conventional culture and sensitivity testing for management of complicated urinary tract infections in adults: part II—evaluation of diagnostic concordance, discordant results, and antimicrobial selection efficacy. *Diagn Microbiol Infect Dis.* 2025;111(3):116646.
5. Kardjadj M, Chang TW, Chavez R, et al. The clinical validity and utility of PCR compared to conventional culture and sensitivity testing for the management of complicated urinary tract infections in adults: a secondary (ad hoc) analysis of pathogen detection, resistance profiles, and impact on clinical outcomes. *Microorganisms.* 2025;13(4):949.
6. Centers for Medicare & Medicaid Services. LCD L39003: MolDX: molecular syndromic panels for infectious disease pathogen identification testing. Effective April 17, 2022. Accessed June 2, 2025. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=39003&ver=10&.
7. Aberger ME, Wilson BA, Chavez R, et al. Evaluating the analytical validity and clinical utility and validity of polymerase chain reaction diagnostics vs culture and sensitivity methods in complicated urinary tract infection management: a comprehensive review of real-world evidence, clinical trials, and meta-analyses concerning molecular diagnostic services program coverage criteria. *Rev Urol.* 2025;24(1).
8. Ko DSC, Lukacz ES, Juster IA, et al. Real-world evidence that a novel diagnostic combining molecular testing with pooled antibiotic susceptibility testing is associated with reduced infection severity and lower cost compared with standard urine culture in patients with complicated or persistently recurrent urinary tract infections. *JU Open Plus.* 2023;1(5):e00021.

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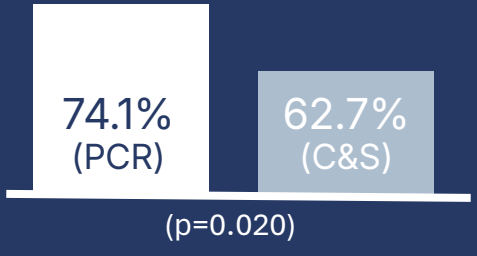
(p<0.001)

Polymicrobial Detection:
43.5% *(PCR) vs 31.9%* ***(C&S)***
(p<0.003)

Clinical Outcomes

Complete Clinical Cure



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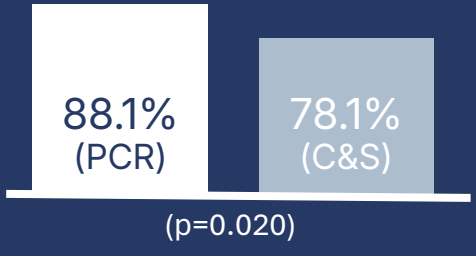
Favorable Clinical Outcomes



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