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CLINICAL CHARACTERISTICS AND EVALUATION OF THE DIAGNOSTIC ACCURACY OF MOLECULAR DIAGNOSTIC TOOLS IN UROGENITAL TUBERCULOSIS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Urogenital tuberculosis (UGTB) represents a principal clinical manifestation of extrapulmonary TB. Diagnosis is frequently delayed due to nonspecific clinical symptoms and limited sensitivity of conventional diagnostic methods.

Methods: This systematic review followed PRISMA guidelines, conducting a comprehensive literature search across PubMed, Embase, Google Scholar, and Cochrane databases. The evaluation focused on patient clinical characteristics and the diagnostic accuracy of GeneXpert (MTB/RIF and Ultra) on urogenital specimens.

Results: The most predominant clinical manifestations of UGTB include flank pain, irritative lower urinary tract symptoms, and sterile pyuria. Molecular tests such as GeneXpert MTB/RIF provide significantly faster results compared to culture (2 hours versus 6–8 weeks). This method demonstrates very high specificity (>90%), although sensitivity varies. The use of GeneXpert Ultra significantly improves detection sensitivity in urine samples with low bacterial burden (paucibacillary).

Conclusion: Integration of accurate clinical findings with current molecular diagnostic technology is critically important. This approach supports early detection to prevent permanent organ damage such as contracted bladder or chronic renal failure.

Keywords: Urogenital Tuberculosis, Molecular Diagnostics, GeneXpert, Diagnostic Accuracy, Clinical Characteristics.

INTRODUCTION

Urogenital tuberculosis (UGTB) is one of the most common forms of extrapulmonary tuberculosis, yet it is frequently overlooked in clinical practice.¹ The clinical manifestations of this disease are highly variable and nonspecific, often mimicking other urological pathologies.² Diagnostic difficulty is further compounded by the low sensitivity of conventional acid-fast bacilli (AFB) smear microscopy and prolonged culture incubation times.³ Significant diagnostic delays frequently occur due to insufficient clinical suspicion and limited access to adequate healthcare facilities.⁴

To address these challenges, various molecular diagnostic technologies such as Xpert MTB/RIF have been developed and demonstrated good efficacy across a range of specimen types.⁵ The use of low-complexity automated nucleic acid amplification tests has become the new standard for detecting extrapulmonary tuberculosis and rifampicin resistance in adults.⁶ In addition, biomarker assays such as urinary lipoarabinomannan (LAM) are increasingly being investigated as rapid diagnostic aids, particularly in patients with specific conditions.⁷ Integration of various diagnostic modalities, including imaging such as computed tomography (CT), remains crucial for anatomical and functional organ involvement assessment.⁸

RESEARCH METHODOLOGY

This study constitutes a systematic review conducted according to PRISMA guidelines through comprehensive searches of PubMed, Embase, Google Scholar, and Cochrane databases. The search strategy employed Boolean operators with relevant keywords such as "urogenital tuberculosis," "diagnostic accuracy," and "molecular diagnostics" for articles in English and Indonesian through 2026. Inclusion criteria encompassed original studies, case reports, and reviews evaluating clinical characteristics and the accuracy of molecular tools (PCR and Xpert MTB/RIF) against gold standards such as culture (MGIT/Lowenstein-Jensen media), histopathology, or Composite Reference Standard (CRS). Manuscript screening was conducted independently through title, abstract, and full-text evaluation, excluding articles without full text or those focusing solely on primary pulmonary TB. Data from selected studies encompassing global populations (China, India, Pakistan, Indonesia, and Brazil) were systematically extracted into dedicated forms recording researcher identity, patient demographics, clinical profiles, and sensitivity and specificity values of diagnostic tools. Included studies demonstrated significant sample size variation, ranging from small-scale (n=8) to mass screening (n=4,368), with a predominance of cross-sectional and retrospective analytical designs. Data synthesis was conducted narratively to integrate clinical findings with the effectiveness of current diagnostic technologies, providing a comprehensive overview of challenges and advances in urogenital tuberculosis diagnosis.

RESULTS

Epidemiology and Clinical Urgency

Urogenital tuberculosis (UGTB) ranks as the second or third most frequently encountered extrapulmonary manifestation clinically, accounting for approximately 30% to 40% of all extrapulmonary TB cases worldwide. The disease develops through hematogenous dissemination of *Mycobacterium tuberculosis* (Mtb) bacilli from the primary pulmonary focus, with the kidney being the most commonly affected organ within the infectious spectrum.^{4,20} Despite its significant prevalence, experts continue to face broad controversy regarding the epidemiology, definition, and classification of this disease due to its extensive spectrum of manifestations, involving the kidneys, entire urinary tract, and both male and female genital organs.²¹

The clinical urgency of UGTB lies in the difficulty of early detection; clinicians frequently miss the diagnosis due to the insidious disease onset and subtle clinical manifestations.²² Yet timely diagnosis and treatment are critically important to halt lesion progression and prevent fatal consequences such as end-stage renal failure.^{3,12} Delayed intervention not only precipitates irreversible organ damage and permanent tissue injury but also significantly increases the risk of infertility.²² Without adequate medical intervention, the prognosis is extremely poor, with two-thirds of infected patients at risk of mortality.²³

Pathophysiology and Mechanisms of Infection

Urogenital tuberculosis (UGTB) develops as a secondary infection precipitated by hematogenous dissemination of *Mycobacterium tuberculosis* (Mtb) bacilli from the primary pulmonary focus to the renal cortex.^{2,24} Although aerosol inhalation constitutes the primary route, other pathways including consumption of *M. bovis*-contaminated dairy products or sexual transmission have also been reported.²² Upon reaching the kidney, bacilli form initial lesions that induce scarring and granuloma formation.²⁵ The disease is characterized by an exceptionally long latent period, with a mean reactivation occurring 20 years after primary infection and a lifetime reactivation risk of up to 15%.^{4,22}

Table 1. Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size (N)	Specimen Type	Reference Standard	Research Findings	Accuracy
Ajantha (2024)⁹	India	Prospective Diagnostic / Cross-sectional Study	80 Patients (plus 15 healthy controls)	Urine	Sputum Culture (MGIT-960) & CBNAAT (GeneXpert)	Urinary Lipoarabinomannan (LAM) measurement effective as diagnostic tool for smear-negative pulmonary TB patients.	vs. Culture: Sensitivity 100%, Specificity 92.3% (Cut-off 0.58 ng/ml).
Ji (2024)¹⁰	China	Retrospective Diagnostic Study	297 (137 Active TB, 160 non-TB)	Blood (MTB-PCR) & Urine (LAM)	Microbiological / Clinical Active TB Diagnosis	Combination of blood-based Host Response test (MTB-PCR) and urine	Combination (MTB-PCR & LAM): Sensitivity 83.21%, Specificity 83.13%.

Author (Year)	Country	Study Design	Sample Size (N)	Specimen Type	Reference Standard	Research Findings	Accuracy
						LAM significantly improves TB diagnostic accuracy.	
Ullah (2025)¹¹	Pakistan	Retrospective Cross-sectional Study	2174	Various EPTB (Pleural, CSF, Tissue, Urine, Pus, etc.)	TB Culture (Solid & Liquid Media)	GeneXpert can detect EPTB cases early for rapid treatment, although negative results do not fully exclude EPTB.	Overall: Sensitivity 67%, Specificity 94%. Urine: Sensitivity 80%, Specificity 99%.
Wang (2022)¹²	China	Cross-sectional Diagnostic Accuracy Study	161 (suspected urogenital TB cases)	Urine	Composite Reference Standard (CRS)	Xpert MTB/RIF outperforms AFB smear and	Xpert: Sensitivity 41.7%, Specificity 85.7%

Author (Year)	Country	Study Design	Sample Size (N)	Specimen Type	Reference Standard	Research Findings	Accuracy
						culture for urinary TB detection.	(calculated from FP ratio 14.3%).
Solanki (2020)¹³	India	Prospective Controlled Cohort Study	160 (68 Spinal TB, 92 Controls)	Tissue (Spinal Biopsy)	Histopathology & AFB Culture	GeneXpert is a highly sensitive, specific, and rapid method for diagnosing spinal tuberculosis (TB spondylitis).	GeneXpert : Sensitivity 91.18%, Specificity 100%.
Li, Y (2025)³	China	Retrospective Analysis	82 (59 Urogenital TB, 23 non-TB)	Urine & Blood	Clinical/Pathological Diagnosis (UTB vs non-UTB)	Combined testing of Urine Leukocytes, Creatinine, TB-DOT, and	Combined 4 Tests: Sensitivity 40.0%, Specificity 100%.

Author (Year)	Country	Study Design	Sample Size (N)	Specimen Type	Reference Standard	Research Findings	Accuracy
						T- SPOT.TB provides strong predictive value for urinary TB infection confirmat ion.	
Li, Z (2025)¹⁴	China	Retrospecti ve Clinical Analysis	217 (145 Typical, 72 Atypical)	Urine & Tissue	Composite Diagnosis (Clinical, Pathological, Lab)	Atypical renal TB manifesta tions differ markedly from typical presentati on (minimal irritative symptoms) , warrantin	Not specificall y reported; TB-DNA PCR positivity rate 26.7%.

Author (Year)	Country	Study Design	Sample Size (N)	Specimen Type	Reference Standard	Research Findings	Accuracy
						g heightene d vigilance and combined testing.	
Xiong (2025)⁷	China	Prospective Cohort Study	130 (80 Pulmonary TB, 50 non- TB)	Urine	AFB Smear & MGIT Culture	Urinary Lipoarabi nomanna n (LAM) is useful both for initial diagnosis and as a treatment response monitorin g model (predictor of sputum conversio n).	Sensitivity : 51–55%, Specificity : 95–100% (based on supporting literature).

Author (Year)	Country	Study Design	Sample Size (N)	Specimen Type	Reference Standard	Research Findings	Accuracy
Christianto (2025) ¹⁷	Indonesia	Cross-sectional Study	55 Patients (RR-TB)	Sputum	GeneXpert MTB/RIF Ultra	High bacteriological burden (based on low CT values) significantly correlates with clinical severity and chest pain.	Significant negative correlation ($r = -0.342$) between smear score and PCR CT value.
Silva (2024) ¹⁶	Brazil	Cross-sectional (Prison Mass Screening)	4368	Sputum	Xpert MTB/RIF Positivity	Sputum specimen quality (especially mucoid/mucopurulent) significantly increases	Overall positivity rate 10.2% (12.0% in mucoid vs 3.7% in saliva samples).

Author (Year)	Country	Study Design	Sample Size (N)	Specimen Type	Reference Standard	Research Findings	Accuracy
						TB diagnostic positivity ratio using Xpert.	
Kiflie (2023)¹⁸	Ethiopia	Deep Learning Study (AI Image Processing)	892 original images (augmented to 8000)	Sputum (Microscopic Images)	Expert Laboratory Labeling	Ensemble visual feature extraction (CNN + GLCM) with KNN algorithm classification is highly optimal for inspecting sputum smear quality.	AI Model Accuracy: 94.0%.
Wicaksono (2021)²	Indonesia	Systematic Review (Evidence-	9 Primary Studies	Urine	Mycobacterial Urine Culture	PCR cannot be used in	Nested PCR IS6110:

Author (Year)	Country	Study Design	Sample Size (N)	Specimen Type	Reference Standard	Research Findings	Accuracy
		Based Case Report)				isolation to diagnose Urogenita l TB, but is strongly recomme nded as a complem ent to culture to guide managem ent.	Sensitivity 95.99%, Specificity 98.11%.
Kay (2020)¹⁹	Global (Cochra ne)	Systematic Review & Meta- analysis	49 Primary Studies	Sputum, Gastric Lavage, Stool, etc.	Microbiologica l Culture & MTBDRplus	Xpert MTB/RIF and Xpert Ultra proven to have high accuracy for TB and rifampici n resistance	Sputum (culture): Sensitivity 64.6%, Specificity 99.0%.

Author (Year)	Country	Study Design	Sample Size (N)	Specimen Type	Reference Standard	Research Findings	Accuracy
						in children.	
Kohli (2025)⁶	Global (Cochrane)	Systematic Review & Meta-analysis	37 Primary Studies (Adults/Adolescents only)	Various EPTB (CSF, Pleural, Tissue, Urine)	Microbiological Reference Standard (MRS) & Composite (CRS)	Low-complexity automated NAATs (e.g., Xpert Ultra) have variable sensitivity on EPTB specimens but with very high specificity.	Urine (CRS): Sensitivity 23.0%, Specificity 98.9%. CSF (MRS): Sensitivity 88.2%, Specificity 96.0%.
Gong (2023)⁵	Global	Systematic Review & Meta-analysis	144 Primary Studies	Sputum, Gastric Lavage, BALF, Stool, Biopsy	Diagnostic Gold Standard (Culture)	Xpert diagnostic tools significantly improve TB	Sputum: Sensitivity 95%, Specificity 96%. Gastric Lavage:

Author (Year)	Country	Study Design	Sample Size (N)	Specimen Type	Reference Standard	Research Findings	Accuracy
						diagnosis accuracy across various specimen s compared to traditional methods.	Sensitivity 94%, Specificity 96%.

The clinical course of UGTB progresses incrementally, from minimal tissue damage to potential end-stage renal failure.²⁶ Parenchymal destruction is specifically precipitated by caseous granuloma formation, fibrosis, and cavitory development that in chronic cases may progress to calcification or abscess formation.^{8,27} Lower urinary tract invasion occurs when papillary granulomas rupture, disseminating bacilli to the ureter and bladder via urinary flow. This lower urinary tract involvement frequently precipitates ureteral stricture formation resulting in hydronephrosis.²⁸

Within the bladder, infection progresses through four pathological stages, from tuberculous infiltration to total obliteration. Extensive fibrosis of the bladder wall and detrusor muscle precipitates the condition known as contracted bladder or "thimble bladder."⁴ In males, infection frequently involves the prostate and epididymis, posing a risk to reproductive function.¹ Given the complexity of these structural changes, identification of anatomical alterations through imaging becomes critically important for determining disease severity.⁸

Clinical Manifestations and Signs and Symptoms

Urogenital tuberculosis (UGTB) is frequently asymptomatic in early stages despite progressive parenchymal renal destruction.^{25,29} The disease has an exceptionally long latent period, frequently exceeding 20 years before clinical reactivation occurs.²² The clinical characteristics of

UGTB demonstrate a broad symptom spectrum (Table 2). Irritative lower urinary tract symptoms represent the most predominant manifestations, including urinary frequency or pollakiuria (50.5% to 95.86% in typical cases), nocturia, and urgency.^{26,28} These complaints are frequently accompanied by hematuria (35.6%) and lower back or pelvic pain (34.4%).²⁰ Laboratorially, sterile pyuria is detected in approximately 89% of patients, a key finding frequently misinterpreted as acute bacterial urinary tract infection (UTI), thereby precipitating diagnostic delay.^{22,23} Microscopic hematuria is detected in 50% of patients, while the macroscopic form is observed in 10% of cases.²²

Specific organ involvement within the urinary tract may progress to interstitial nephritis and end-stage renal failure if bilateral involvement occurs.^{22,25} Within the bladder, chronic inflammation induces fibrosis and detrusor muscle contraction that drastically reduces functional capacity to below 100 mL, a condition designated as "thimble bladder."⁴ This damage is frequently accompanied by complications including ureteral stricture with the characteristic radiological appearance of a "pipe-stem" or "beaded" pattern, hydronephrosis, and vesicoureteral reflux.²² Conversely, systemic constitutional symptoms such as fever, night sweats, and weight loss (13.5%) are rarely encountered in isolation and typically indicate an active tuberculosis focus outside the urogenital system.^{2,22}

In the reproductive system, female UGTB is frequently non-aggressive and typically identified during infertility evaluation in endemic regions. Clinical manifestations may include menstrual disturbances, adnexal masses, or elevated CA-125 levels mimicking ovarian malignancy. In males, prostatic involvement is generally asymptomatic and frequently discovered incidentally via prostate biopsy, although it may cause azoospermia and perineal fistula.²² Scrotal involvement may present as epididymal induration or nontender firm nodules, which risk precipitating infertility due to ejaculatory duct fibrosis.^{22,26} Other genital lesions such as penile ulcers or complex urethral strictures known as "watering-can perineum" are relatively rare but necessitate careful differential diagnosis from malignancy and sexually transmitted infections.²²

Table 2. Summary of Clinical Characteristics of UGTB Patients

Symptom/Clinical Sign	Frequency (%)	Reference / Notes
Irritative Symptoms (Pollakiuria)	50.5%	Review of nearly 9,000 patients from 33 case series. ²⁴
Irritative Symptoms (Frequency/Urgency)	95.86% (Frequency) 72.41% (Urgency)	In patients with "Typical" UGTB manifestations. ¹⁴
Hematuria	35.6%	One of three principal UGTB symptoms. ²⁴
Hematuria (Typical/Atypical)	25.5% (Typical) 6.9% (Atypical)	Frequency varies depending on typical or atypical clinical presentation. ¹⁴
Low Back Pain	34.4%	Second principal symptom after urinary frequency. ²⁴
Flank Pain	18.8%	Specific to patients with urinary/renal TB. ²⁹
Pyuria (Leukocyturia)	46%	Review study citing general clinical prevalence. ²
Sterile Pyuria	N/A (Qualitative)	Identified as a key finding frequently overlooked or misdiagnosed as ordinary bacterial UTI. ⁴
Weight Loss	13.5%	Constitutional (systemic) symptoms less common than local symptoms. ²⁹
Constitutional Symptoms	N/A (Qualitative)	Cited as general constitutional symptoms alongside fever and night sweats. ³⁰

Diagnostic Strategy and Accuracy Evaluation

Selection of diagnostic methods for Urogenital Tuberculosis (UGTB) is multidimensional, contingent upon facility availability, cost, degree of clinical suspicion, and patient renal function. Given the frequently paucibacillary nature of the disease (low bacterial burden), diagnosis usually

requires integration of at least one or more Mycobacterium tuberculosis (Mtb) identification tests, wherein positive culture remains acknowledged as the definitive gold standard.^{2,22}

Smear Microscopy and Histological Examination

To date, histopathology and acid-fast bacilli (AFB) smear microscopy remain first-line tools due to their accessibility. Urine smear microscopy utilizing Ziehl-Neelsen or auramine staining demonstrates high specificity of up to 96.7%, yet its sensitivity is very low, ranging from 42.1% to 52.1%.² The reliability of this test is highly dependent on bacterial burden exceeding 10,000 organisms/mL and is susceptible to observer error.²² Meanwhile, histological examination via biopsy or fine-needle aspiration biopsy (FNAB) serves as a vital adjunct for identifying epithelioid granulomas or caseous necrosis. Although histopathology is time-consuming and demands high technical expertise, this method is invaluable in diagnosing difficult cases such as prostatic or ovarian TB that frequently mimic malignancy.^{13,22}

Urinalysis Microscopy and Lipoarabinomannan (LAM) Biomarker

Urinalysis represents the least invasive diagnostic method. The most characteristic laboratory finding is sterile pyuria — the presence of leukocytes in urine without bacterial growth on standard culture media.^{2,3} Microscopic analysis of 24-hour urine sediment can yield positive results in up to 90% of renal TB cases, although specificity may be compromised by nontuberculous mycobacteria.²²

Recent innovations involve detection of the Lipoarabinomannan (LAM) antigen, a glycolipid of the Mtb cell wall released into urine during active infection. The lateral-flow urine LAM assay (LF-LAM) employs nanogold-labeled antibodies to capture this glycolipid. This method is particularly beneficial in populations with severe immunosuppression (HIV) or in children unable to provide sputum samples.^{9,31} Although its sensitivity is generally moderate (approximately 58.75%), urinary LAM demonstrates positive correlation with disease severity and holds significant potential for dynamically monitoring patient response to antituberculosis therapy.^{7,10}

Mycobacterium tuberculosis Culture

Culture remains the absolute gold standard with 100% specificity. Solid Lowenstein-Jensen media requires up to 6–8 weeks to confirm negative results, whereas automated liquid

media systems such as Mycobacteria Growth Indicator Tube (MGIT) are considerably faster, yielding positive results within 9 to 10 days.^{7,22} The advantages of liquid culture include higher sensitivity, the ability to identify specific species, and enabling phenotypic drug susceptibility testing. However, urine culture is frequently hampered by the sporadic nature of bacilluria, necessitating collection of at least 3 to 5 consecutive early morning urine specimens to achieve diagnostic sensitivity of 80% to 93%.^{22,27}

Molecular Testing and Diagnostic Innovations

Molecular technology has revolutionized the speed of Urogenital Tuberculosis (UGTB) diagnosis compared to traditional culture methods.² Nucleic Acid Amplification Test (NAAT)-based assays can provide accurate results within less than 24 hours while simultaneously detecting rifampicin resistance.¹³ The WHO progressively approved PCR use for sputum samples in 2010, followed by approval for non-respiratory samples in extrapulmonary tuberculosis (EPTB) diagnosis in 2013.²²

Polymerase Chain Reaction (PCR) and AFB PCR

Acid-fast bacillus polymerase chain reaction (AFB PCR) is a laboratory technique that amplifies specific DNA sequences of *Mycobacterium tuberculosis* (Mtb), enabling bacterial detection even at low concentrations in urine or tissue biopsy samples.³² PCR testing offers several advantages including rapid detection within less than 2 hours, minimal risk of cross-contamination, and relatively affordable cost.²²

PCR sensitivity varies between 80% and 95% depending on regional endemicity. Compared to culture, PCR demonstrates sensitivity of 95.6% and specificity of 98.1%. However, in UGTB-specific studies, PCR sensitivity in urine samples was reported at 63%, while in endometrial biopsies from infertile women it reached only 46.6%.²² Recent PCR technique innovations demonstrate a sensitivity range of 25–93% with very high specificity (95–100%).² Use of specific primers such as IS6110, MPT64, and 16S rRNA in urine samples yields pooled sensitivity of 88.6% and specificity of 96.5% compared to urine culture.³⁰ Although highly accurate when positive, a negative PCR reading does not categorically exclude UGTB.²²

Efficacy of the GeneXpert MTB/RIF and Xpert Ultra Platforms

The GeneXpert MTB/RIF system is a fully automated hemi-nested real-time PCR platform that detects mutations in the 81-bp core region of the *rpoB* gene using five molecular beacons for rifampicin resistance identification within less than 3 hours.³³ This platform demonstrates variable sensitivity ranging from 80% to 90% across various extrapulmonary specimens.¹³

The latest generation, Xpert MTB/RIF Ultra, has significantly enhanced diagnostic power, particularly in patients with paucibacillary disease (low bacterial burden) due to its lower limit of detection.^{6,10} Xpert Ultra has proven effective for rapid diagnosis in urine and tissue samples, with estimated general specificity exceeding 98%.^{5,19} However, this platform has technical limitations; it is highly dependent on sample quality, and results may be compromised in patients providing poor-quality samples.^{16,18} Furthermore, high costs and complex laboratory infrastructure requirements render this technology frequently unavailable at primary healthcare settings.^{10,34}

Comparison with Conventional Methods and Biomarker Integration

Compared to liquid (MGIT) or solid (Lowenstein-Jensen) culture media requiring 6–8 weeks, molecular methods offer crucial time efficiency for preventing irreversible renal function damage.^{2,25} Urine AFB smear microscopy frequently fails due to intermittent bacterial excretion and requires minimum bacterial burden of 10,000 organisms/mL.^{9,22}

Integration of molecular tests with biomarkers such as urinary lipoarabinomannan (LAM) can enhance diagnostic power, particularly for HIV patients or children unable to provide sputum.^{7,31} Combination of NAAT results with urine leukocyte testing, IGRA, and clinical findings remains the primary basis for medical decision-making.^{2,3} Future innovations such as whole-genome sequencing (WGS), targeted next-generation sequencing (NGS), and cell-free DNA detection in urine promise enhanced identification of drug resistance and more detailed characterization of transmission patterns.^{22,31}

Evaluation of Molecular Diagnostic Tool Performance

Evaluation of molecular diagnostic tool performance demonstrates that Nucleic Acid Amplification Test (NAAT)-based technologies possess promising accuracy, although it remains variable across methods and specimen types (Table 3). Several studies support these findings, including Ghaleb et al. (2013) who reported that PCR provides higher detection rates compared to

conventional smear and culture, with sensitivity and specificity each reaching 100%, rendering it highly reliable for early genitourinary tuberculosis diagnosis.³⁵ The Xpert MTB/RIF assay in urine specimens is reported to have sensitivity ranging from 60.7% to 80% with very high specificity, even reaching 99.4%, along with the additional advantage of short examination time and ability to detect rifampicin resistance, as demonstrated by Kanade et al. (2023) in genital TB with 100% specificity.³⁶

In specific tissues such as spinal tissue, Xpert accuracy was reported to reach 91.18% with absolute 100% specificity. In addition, tissue PCR also demonstrated good diagnostic performance with sensitivity and specificity of 87.5% and 86.7% respectively, and faster diagnosis time compared to histopathology.³⁷ Nested PCR targeting the IS6110 gene in urine specimens demonstrated superior performance, with sensitivity of 95.99% and specificity of 98.11%, surpassing 16SrRNA targets, while real-time PCR is reported to have high sensitivity albeit with moderate specificity.³⁸ Overall, the reliability of these molecular methods is reinforced by the meta-analysis of Altez-Fernandez et al. (2017) reporting pooled sensitivity of 0.87 and specificity of 0.91, and by findings that Xpert Ultra demonstrates superior efficacy in detecting rifampicin resistance with 100% sensitivity, affirming the central role of NAAT in accurate and timely UGTB diagnosis.³⁹

Table 3. Molecular Diagnostic Performance (Sensitivity & Specificity)

Tool Name (Specimen)	Sensitivity (%)	Specificity (%)	PPV / NPV (%)
Xpert MTB/RIF (Adult Sputum) ⁵	95%	96%	—
Xpert MTB/RIF (Pediatric Sputum) ¹⁹	64.6%	99.0%	—
Xpert Ultra (Pediatric Sputum) ¹⁹	72.8%	97.5%	—
Xpert MTB/RIF (Urine) ¹¹	80%	99%	PPV: 67% / NPV: 99%
Xpert MTB/RIF (Urine) ¹²	78.9%	68.6%	PPV: 41.7% / NPV: 88.2%*

Xpert MTB/RIF (Urine)²⁴	60.7%	99.4%	–
Nested PCR IS6110 (Urine)²	95.99%	98.11%	PPV: 96.6% / NPV: 97.5%
PCR 16SrRNA (Urine)²	87.05%	98.9%	PPV: 97.8% / NPV: 93.1%
Xpert Ultra (Cerebrospinal Fluid)⁶	88.2%	96.0%	–
Xpert MTB/RIF (Cerebrospinal Fluid)³⁰	70%	97%	–
Xpert Ultra (Pleural Fluid)⁶	74.0%	88.1%	–
Xpert MTB/RIF (Spinal Tissue)¹³	91.18%	100%	PPV: 100% / NPV: 93.9%
Xpert Ultra (Rifampicin Resistance Detection)⁶	100%	99.4%	–
Xpert MTB/RIF (Pus)¹¹	91%	87%	PPV: 67% / NPV: 97%

Table 4. Pre-analytical Procedures: Sample Collection & Processing

Pre-analytical Aspect	Recommendations / Standards
Collection Time^{3,7,25}	Urine: First-morning, midstream void to maximize bacillary concentration. Sputum: Morning sputum, spot sputum, or overnight sputum.
Minimum Volume^{6,7,10,16}	Urine: ≥10 mL to ≥15 mL. Sputum: 2 mL (minimum), 3–5 mL recommended. Blood (Fingerstick): ≥100 µL. Cerebrospinal Fluid (CSF): >6 mL recommended to enhance Xpert Ultra sensitivity.
Collection Frequency^{4,16,25}	Urine: 3 consecutive morning samples (especially for culture to address paucibacillary nature). Sputum: Spot collection used in mass screening.
Centrifugation Speed^{7,9,11,12}	For TB Culture (Urine/Other Fluids): 3000 × g for 15 minutes. For Decontamination (NALC-NaOH Method): 4000 × g for 15 minutes. For

	ELISA/LAM Testing: 2000 rpm for 20 minutes or $300 \times g$ for 5 minutes.
Storage Temperature^{3,7,9}	Short-term: 2°C–8°C (Refrigerated) if not immediately processed (maximum 7 days). Long-term: –20°C to –80°C (for supernatant or archived samples).
Decontamination Method^{6,11,41}	NALC-NaOH Method: Used for non-sterile specimens (sputum, urine) prior to culture to eliminate non-TB bacteria. Sterile specimens (CSF) are generally not decontaminated.

Influence of Pre-analytical Procedures and Cost-Effectiveness

The success of molecular and microbiological diagnosis is highly dependent on pre-analytical standardization (Table 4). Use of first-morning urine specimens with minimum volume of 10–15 mL is recommended due to nocturnal bacterial accumulation.^{2,10} Sediment concentration via centrifugation at $3000\text{--}4000 \times g$ for 15 minutes significantly enhances DNA detection probability.¹² The use of pooled urine samples over three consecutive days has also been reported to increase sensitivity.⁴⁰ Economically, implementation of molecular tools has proven cost-effective through reduction of unnecessary invasive diagnostic procedures and decreased long-term surgical complication rates.^{14,25}

Radiological Ancillary Examinations

Radiological imaging plays a crucial role in assessing anatomical changes, fibrosis, calcification, and tissue destruction in urogenital organs. Collectively, imaging techniques demonstrate sensitivity of up to 91.4% in establishing the radiological diagnosis of UGTB.^{22,30}

Computed Tomography (CT) and CT Urography

CT scan or CT urography remains the primary modality of choice with sensitivity exceeding 90% due to its capacity for more detailed anatomical delineation compared to intravenous urography (IVU) or ultrasonography (Table 5). CT is particularly effective in detecting cortical masses, granulomas, and calcifications throughout the urinary tract found in more than 50% of patients. Characteristic renal findings include intrarenal hypodense foci, hydronephrosis, scarring, and renal atrophy. In advanced stages, peripheral renal lobular calcifications due to

papillary necrosis may result in "putty kidney" (autonephrectomy) formation, a condition rarely occurring without a prior history of pulmonary tuberculosis.^{8,22}

Furthermore, CT urography can identify three primary characteristic findings of UGTB: (1) simultaneous renal and bladder lesions, (2) intrarenal infundibular strictures, and (3) low attenuation lesions in the renal cortex. Bladder involvement is characterized by wall thickening with calcification in the contracted fibrotic bladder (thimble bladder with capacity ≤ 20 mL). Adrenal involvement may also be detected via bilateral enlargement with peripheral enhancement, frequently accompanying Addison's disease.²²

Conventional Radiography and Specialized Urography

Conventional radiography and specialized urography play important roles in urogenital tuberculosis (UGTB) evaluation. Chest radiography is mandatory in all patients with suspected UGTB to identify possible concurrent pulmonary infection; approximately 13.5% to 27% of patients exhibit pulmonary abnormalities, although paradoxically up to 50% of UGTB patients may have completely normal chest radiographs. Intravenous urography (IVU) and pyelography, although partly superseded by CT, remain considered the classic standard for detecting early UGTB, particularly through calyceal deformity with the characteristic "moth-eaten" appearance from erosion, and ureteral changes including the "pipe-stem" pattern, "beaded" pattern, or saw-tooth appearance. Hysterosalpingography is recognized as the gold standard for detecting isolated female genital tuberculosis in infertile women, with findings including intrauterine adhesions, rigid fallopian tubes, and adnexal lymph node calcification, rendering it a crucial examination albeit less patient-friendly.²²

Ultrasonography (USG) and MRI

Ultrasonography is most suitable for evaluating scrotal, testicular, and epididymal involvement, as well as monitoring hydronephrosis progression. Characteristic findings include tubo-ovarian masses in women, and heterogeneous epididymal thickening and miliary lesion patterns on the male testis. Magnetic Resonance Imaging (MRI) is particularly useful for evaluating genital soft tissues and the prostate. Prostatic tuberculosis on MRI is demonstrated by low T2-signal intensity radiating areas, known as the "watermelon skin" sign. MRI also excels in detecting sinuses, fistulae, and abdominal peritonitis.²²

Cystoscopy and Tissue Biopsy

Diagnostic cystoscopy frequently demonstrates focal erythema, granulomas, and "golf-hole" ureteral orifices indicating severe fibrosis and risk of vesicoureteral reflux. Bladder biopsy during cystoscopy has sensitivity of 18.5% to 52%. Although histopathology can identify caseous necrosis, definitive confirmation still requires the presence of Mtb on culture or molecular testing.²²

Table 5. Role of Ancillary Examinations (Radiology & Other Laboratory Tests)

Examination Type	Characteristic UGTB Findings	Diagnostic Role
CT Scan / CT Urography ^{8,14,25}	Intrarenal Calcifications: Granular or curvilinear. Parenchymal Destruction: Moth-eaten calyces (serrated calyceal margins), papillary necrosis, autonephrectomy (putty kidney). Structural: Ureteral/bladder wall thickening, hydronephrosis.	Preferred imaging modality (current standard) due to high sensitivity (>90%) for detecting subtle calcifications and assessing extent of anatomical damage not visible on USG or IVU.
IVU / IVP (Intravenous Urography) ^{14,25,29}	Calyceal Deformity: "Moth-eaten" appearance from erosion. Obstruction: Ureteral strictures, phantom calyx (unfilled calyx), rigid (pipe-stem) or irregular (beaded) ureter.	Classic standard for visualizing excretory function and urinary tract anatomical details; highly useful for detecting early ureteral mucosal lesions.
Routine Laboratory (Blood & Urine) ²⁻⁴	Sterile Pyuria: Leukocytes (+) without bacteria on routine culture. Hematuria: Microscopic or macroscopic. Inflammatory Markers: Elevated ESR and CRP.	Initial indicator of clinical suspicion (red flag). Elevated urine leukocytes correlate positively with probability of Urogenital TB diagnosis.
Immunological (T-SPOT.TB / IGRA) ^{3,30}	Reactive/Positive: T-cell response to specific TB antigens. High Sensitivity:	Highly sensitive adjunctive tool, particularly useful when culture is negative or tissue biopsy is

	T-SPOT.TB has ~90% sensitivity for TB infection.	difficult to obtain. More specific than Mantoux skin test.
Biomarker (Urinary LAM) ^{6,7,9}	Positive Antigen: Lipoarabinomannan detection in urine. Level Dynamics: Concentration decreases with successful therapy.	Potential non-invasive diagnostic method and treatment response monitoring tool. Useful in HIV+ patients or paucibacillary cases.
MRI (Magnetic Resonance Imaging) ^{25,29}	Prostatic Pattern: Nodular (T2 hypointense) vs. diffuse type. Abscess: Visualization of cold abscess in soft tissues (e.g., epididymis, psoas).	Superior alternative for soft tissue evaluation (prostate/genitalia) and in patients with renal impairment (avoiding CT iodinated contrast).

Laboratory Examinations

Routine Urinalysis and Bacterial Culture

Urinalysis is found to be abnormal in more than 90% of UGTB patients, typically presenting as sterile pyuria (leukocyturia without bacterial growth on standard culture) in an acidic medium (acid urine). Persistent sterile pyuria or symptomatic UTI unresponsive to standard antibiotics constitutes a strong indicator for suspecting UGTB. The sensitivity of urine sediment microscopy for AFB is 42% to 52% with specificity of 97%.^{2,22}

Immunological Testing and Specific Laboratory Tests

Immunological and specific laboratory tests serve as important complements in establishing the UGTB diagnosis, although none can independently serve as the definitive determinant. Interferon-Gamma Release Assay (IGRA) demonstrates variable sensitivity ranging from 52.6% to 94% in individuals with confirmed UGTB, rendering it highly beneficial as an initial screening tool, particularly in BCG-vaccinated patients; however, negative results cannot categorically "exonerate" patients from the possibility of active disease (Roddy, 2024). The tuberculin skin test (PPD), which operates through delayed-type hypersensitivity mechanisms, serves a similar role as a screening tool, but is also not recommended as the sole basis for active

TB diagnosis (Roddy, 2024). Routine laboratory examinations frequently reveal nonspecific abnormalities, including anemia in 83.04% of patients, hypoalbuminemia in 58.10%, hyponatremia in 50.93%, and elevated C-reactive protein as a disease activity marker; as part of a comprehensive approach, HIV and hepatitis screening is recommended in all patients with positive Mycobacterium tuberculosis results, as coinfections often present without warning yet carry significant clinical consequences.²²

Management of Urogenital Tuberculosis

Pharmacological Management

Treatment of urogenital tuberculosis should be initiated promptly after microbiological or histological diagnosis is established. Under certain circumstances, therapy may be initiated based on strong clinical, laboratory, and radiological suspicion before definitive confirmation is available.²² The cornerstone of treatment is the WHO standard antituberculosis drug (ATD) regimen. For drug-susceptible cases, therapy requires 6–9 months duration, while patients with severe disease, immunosuppression, or malnutrition frequently require durations exceeding 9 months to suppress recurrence risk that may reach 22%.^{26,42}

The treatment regimen employs a combination of bactericidal drugs (isoniazid, rifampin, pyrazinamide, streptomycin) and bacteriostatic agents (ethambutol, ethionamide). The most conservative approach is a four-drug regimen to minimize recurrence risk reaching 80% with monotherapy.²⁶ In Multi-Drug Resistant TB (MDR-TB) cases, therapy requires 12 to 24 months with close monitoring for toxic adverse effects.^{17,42} Although pharmacotherapy can cure small renal foci, the healing response of fibrosis may exacerbate urinary tract obstruction in the early weeks. Therefore, double-J stent placement is strongly considered to prevent renal dysfunction due to ureteral stenosis. Long-term follow-up of up to 10 years is strongly recommended due to the potential for microbiological recurrence that may occur on average 5.3 years post-therapy.²⁶

Surgical Management

Surgical management serves as a crucial adjunctive therapy in UGTB with severe structural complications, with reported rates of surgical intervention requirement reaching 54.9% of patients.⁴² Ideally, surgical procedures are performed after 4 to 6 weeks of antituberculosis drug (ATD) initiation to reduce the risk of systemic bacillary dissemination.²⁶ Ablative procedures

include nephrectomy for severely damaged kidneys, autonephrectomy, total destruction, or those accompanied by persistent hypertension and pain, while epididymectomy is indicated in cases of abscess or scrotal fistula not adequately responding to ATD.^{22,25} Reconstructive procedures encompass pyeloureteral or uretero-ureteral anastomosis, ureteral replacement using an ileal segment for stricture management, and cystoplasty augmentation aimed at increasing bladder capacity in thimble bladder conditions to improve urinary storage function.^{26,28} Specific surgical indications include abscess formation, progressive hydronephrosis, infertility due to reproductive tract stricture, and underlying malignancy suspicion, while minimally invasive techniques such as laparoscopy are increasingly being applied to accelerate patient recovery without compromising procedural effectiveness.^{22,28}

CONCLUSIONS

Synthesis of Clinical Findings and Evaluation of Diagnostic Technology

This systematic review affirms that UGTB remains a principal clinical challenge due to its "occult" manifestations mimicking ordinary bacterial urinary tract infection. The combination of irritative lower urinary tract symptoms and sterile pyuria constitutes the key parameters that should heighten clinical vigilance.^{2,40}

Superiority of Molecular Technology

Accuracy evaluation demonstrates significant superiority of molecular (NAAT) platforms over traditional microscopy. The use of Xpert Ultra significantly enables Mtb detection in paucibacillary urine specimens and provides rapid rifampicin resistance detection.^{6,17} Implementation of NAAT as the first-line test is critically important in routine diagnostic algorithms to initiate therapy earlier and prevent permanent anatomical damage.^{13,43}

Role of Biomarkers and Radiology

Urinary LAM biomarkers offer a non-invasive screening solution sensitive to bacterial burden, rendering it an important modality in HIV and pediatric populations.^{7,31} The synergy between molecular technology and detailed imaging such as CT urography enables detailed mapping of anatomical damage, ultimately reducing the need for complex reconstructive surgical procedures when diagnosed earlier.^{8,25}

Overall, UGTB elimination demands a multidisciplinary approach integrating high clinical vigilance, global accessibility of molecular diagnostic technology, and long-term therapy adherence to prevent irreversible organ function failure.^{4,11}

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