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Original Research Article

Comparative Diagnostic Performance of Conventional DST, Line Probe Assay, and GeneXpert MTB/RIF in Extrapulmonary Tuberculosis Cases

Mayuri K. S.[1], Elavarthi Srikaanth Reddy[2], Bhawini Vijayvergia[3]

[1]Associate Professor, Department of Microbiology, Sir Seewoosagur Ramgoolam Medical college Mauritius.

[2]Associate Professor, Department of Community medicine, GSL Medical College, Rajahmundry, Andhra Pradesh

[3]Assistant Professor, Department of Microbiology, Gmc Chittorgarh, Rajasthan- 312025

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Corresponding Author: Dr. Mayuri K S

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Abstract

Background: Extrapulmonary tuberculosis (EPTB) poses significant diagnostic challenges due to its paucibacillary nature and diverse clinical presentations. Rapid and accurate detection, along with early identification of drug resistance, is essential for effective disease management. Molecular diagnostic tools such as GeneXpert MTB/RIF and Line Probe Assay have emerged as important alternatives to conventional methods.

Methods: A cross-sectional observational study was conducted among 294 patients with suspected extrapulmonary tuberculosis. Clinical specimens were subjected to smear microscopy, culture with drug susceptibility testing (DST), GeneXpert, and Line Probe Assay. Diagnostic performance parameters including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using both composite reference standard (CRS) and culture-based methods.

Results: GeneXpert demonstrated higher sensitivity (87.5% using CRS; 83.9% vs culture) compared to LPA (81.2% and 78.0%, respectively), while LPA showed higher specificity (93.5% vs CRS; 92.0% vs culture). GeneXpert showed superior detection in smear-negative (31.9%) and HIV-positive cases (64.7%). Rifampicin resistance detection was comparable across culture DST (19.6%), GeneXpert (18.8%), and LPA (20.2%), with substantial agreement ($\kappa = 0.69–0.74$; $p < 0.001$).

Conclusion: GeneXpert is a highly sensitive and rapid diagnostic tool for extrapulmonary tuberculosis, while LPA provides higher specificity and reliable resistance detection. Integration of molecular diagnostics with conventional culture methods can significantly improve early diagnosis and management of EPTB.

Keywords: Extrapulmonary tuberculosis; GeneXpert MTB/RIF; Line Probe Assay; Drug susceptibility testing; Rifampicin resistance.

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Introduction

Extrapulmonary tuberculosis (EPTB) constitutes a significant proportion of the global tuberculosis (TB) burden and remains a major diagnostic challenge [1]. According to the World Health Organization, TB continues to be one of the leading infectious causes of mortality worldwide, with an estimated 10.6 million new cases reported annually, of which approximately 15–20% are extrapulmonary, rising to over 50% among immunocompromised individuals, particularly those with HIV infection [2]. In India, which accounts for the highest TB burden globally, EPTB represents nearly 20–25% of all notified TB cases, with lymph node, pleural, abdominal, and osteoarticular involvement being the most common forms [3]. The diagnosis of EPTB is inherently complex due to its paucibacillary nature, diverse clinical presentations, and difficulty in obtaining appropriate specimens [4]. Conventional diagnostic methods such as smear microscopy and culture-based drug susceptibility testing (DST) have long been considered reference standards [5]. However, smear microscopy demonstrates low sensitivity in EPTB (often <30%), while culture, though more sensitive, is time-consuming, requiring several weeks for growth and subsequent DST results [5]. The delay in diagnosis contributes to ongoing morbidity, increased risk of complications, and continued transmission in certain forms [5]. In recent years, rapid molecular diagnostic techniques have revolutionized TB detection and drug resistance profiling [6]. The GeneXpert MTB/RIF assay, endorsed by the WHO, enables simultaneous detection of *Mycobacterium tuberculosis* and rifampicin resistance within two hours, with reported sensitivity ranging from 50–80% in EPTB depending on sample type [7]. Similarly, Line Probe Assay (LPA) allows rapid identification of resistance to first-line anti-tubercular drugs such as isoniazid and rifampicin by detecting mutations in specific genes (e.g., *rpoB*, *katG*, *inhA*) [8]. Despite their advantages, these molecular methods have limitations, including variable sensitivity in paucibacillary specimens, inability to detect resistance beyond targeted genes, and requirement for specialized laboratory infrastructure [9].

Conventional culture-based DST, although considered the gold standard for comprehensive drug resistance profiling, suffers from prolonged turnaround time and biosafety constraints. Moreover, discrepancies between phenotypic and genotypic methods have been reported, particularly in cases with heteroresistance or rare mutations [10]. Therefore, comparative evaluation of these diagnostic modalities is crucial to determine their relative performance, concordance, and clinical utility in EPTB settings. Given the diagnostic dilemmas associated with EPTB and the increasing emphasis on early detection of drug-resistant TB under national programs such as the National Tuberculosis Elimination Programme, there is a pressing need to assess and compare the effectiveness of conventional and molecular diagnostic tools [11]. This study aimed to evaluate the diagnostic performance of conventional drug susceptibility testing, Line Probe Assay, and GeneXpert in extrapulmonary tuberculosis cases, thereby providing evidence to optimize diagnostic algorithms and improve patient outcomes.

Materials and Methods

Study design and setting: This cross-sectional observational study was conducted in the Department of Microbiology in collaboration with the Departments of Pulmonary Medicine and General Medicine at a tertiary care teaching hospital in central India. The study was carried out over a period of 24 months (between July 2023 to June 2025), during which consecutive patients clinically suspected of extrapulmonary tuberculosis (EPTB) were evaluated. Laboratory procedures were performed in an intermediate reference laboratory (IRL) certified under the National Tuberculosis Elimination Programme, following standardized biosafety and quality control protocols.

Study population and sample size: All patients presenting with clinical, radiological, or biochemical suspicion of EPTB were considered eligible. A total of 294 patients were enrolled using a consecutive sampling method to minimize selection bias. Both newly suspected and previously treated cases were included, provided adequate extrapulmonary specimens could be obtained.

Inclusion and exclusion criteria: Patients of all age groups and both sexes with suspected EPTB involving sites such as lymph nodes, pleura, abdomen, central nervous system, bones, joints, or genitourinary tract were included. Only those patients from whom adequate clinical specimens could be collected for all three diagnostic modalities—conventional culture with drug susceptibility testing (DST), Line Probe Assay, and GeneXpert MTB/RIF—were enrolled. Patients already on anti-tubercular therapy for more than two weeks, those with inadequate or contaminated samples, and patients who declined consent were excluded from the study.

Specimen collection and processing: Extrapulmonary specimens were collected from clinically suspected sites by trained clinicians under strict aseptic precautions. These included fine-needle aspiration cytology (FNAC) samples from lymph nodes, pleural, ascitic, and synovial fluids obtained by sterile aspiration, cerebrospinal fluid (CSF) collected via lumbar puncture, pus from abscesses, and tissue biopsies obtained during surgical or image-guided procedures. A minimum volume of 2–5 mL was ensured for fluid samples wherever feasible to allow parallel testing. All specimens were transported to the microbiology laboratory within 1–2 hours of collection in sterile, leak-proof containers, maintaining cold chain (2–8°C) when delay was anticipated.

On receipt, samples were logged and processed in a biosafety cabinet class II following standard biosafety protocols. Non-sterile specimens (pus, tissue homogenates) were subjected to digestion and decontamination using the N-acetyl-L-cysteine–sodium hydroxide (NALC–NaOH) method (final NaOH concentration 1–1.5%), followed by neutralization with phosphate buffer (pH 6.8) and centrifugation at 3000 × g for 15–20 minutes. The resulting pellet was reconstituted in buffer and used for further testing. Sterile body fluids such as CSF were concentrated directly by centrifugation without decontamination. Tissue samples were first mechanically homogenized using a sterile mortar and pestle or tissue grinder before processing.

Smear microscopy was performed using Ziehl–Neelsen staining, and slides were examined under oil immersion for acid-fast bacilli (AFB), graded as per standard reporting criteria. The processed specimen was then aliquoted under aseptic conditions for culture, molecular testing, and drug susceptibility testing to avoid repeated freeze–thaw cycles and contamination.

Conventional culture and drug susceptibility testing: Processed samples were inoculated onto both solid and liquid culture systems to enhance yield. For solid culture, 0.2–0.5 mL of the processed specimen was inoculated onto Lowenstein–Jensen (LJ) medium slants and incubated at 37°C. Cultures were examined weekly for growth for a maximum duration of 8 weeks. In parallel, 0.5 mL of the specimen was inoculated into Mycobacteria Growth Indicator Tube (MGIT) 960 liquid culture system, supplemented with OADC enrichment and PANTA antibiotic mixture to suppress contaminants. MGIT tubes were incubated and continuously monitored in the automated system for fluorescence-based detection of growth, with positivity typically flagged within 7–21 days.

Positive cultures from either system were confirmed as Mycobacterium tuberculosis complex using rapid immunochromatographic assays detecting the MPT64 antigen or standard biochemical tests where required. Contaminated cultures were excluded and repeat sampling was requested when feasible.

Phenotypic drug susceptibility testing (DST) was performed on culture isolates using the proportion method on LJ medium or MGIT-based DST, following standard critical concentrations (isoniazid: 0.2 µg/mL; rifampicin: 40 µg/mL for LJ or equivalent MGIT concentrations). Growth of ≥1% of bacilli in the presence of the drug compared to the control was interpreted as resistance. Culture-based DST results were considered the reference standard for evaluating diagnostic performance.

Molecular diagnostic methods: The GeneXpert MTB/RIF assay was performed directly on processed or unprocessed specimens depending on sample type, strictly adhering to manufacturer instructions. Briefly, a defined volume of specimen was mixed with sample reagent in a 2:1 ratio, incubated for 10–15 minutes for liquefaction and inactivation, and then transferred into a single-use cartridge. The assay was run on the GeneXpert platform, which performs automated DNA extraction, amplification, and real-time PCR detection. Results were generated within approximately 2 hours and reported as MTB detected/not detected, along with rifampicin resistance status (detected/indeterminate/not detected) based on mutations in the rpoB gene.

For Line Probe Assay (LPA), DNA extraction was performed either directly from smear-positive specimens or from culture isolates in smear-negative cases to improve sensitivity. The assay (Genotype MTBDRplus, Hain Lifescience) involved multiplex PCR amplification followed by reverse hybridization on nitrocellulose strips containing probes targeting wild-type and mutant regions of the rpoB, katG, and inhA genes. Hybridization, washing, and color development steps were carried out as per standardized protocols. Banding patterns were interpreted using the manufacturer's reference chart, and resistance was inferred based on the absence of wild-type bands and/or presence of mutation-specific bands. Internal controls, including amplification and conjugate controls, were used to validate each run.

Outcome measures and definitions: A case of EPTB was considered microbiologically confirmed if Mycobacterium tuberculosis was detected by any of the diagnostic methods. Rifampicin resistance detected by GeneXpert or LPA was interpreted as a surrogate marker for multidrug-resistant TB (MDR-TB), in accordance with WHO recommendations. Diagnostic performance parameters, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated for GeneXpert and LPA using conventional culture-based DST as the reference standard.

Statistical analysis: Data were entered into Microsoft Excel and analyzed using statistical software such as SPSS version 20.0. Categorical variables were expressed as frequencies and percentages, while continuous variables were summarized as mean ± standard deviation. Diagnostic accuracy indices (sensitivity, specificity, PPV, NPV) were calculated with 95% confidence intervals. Agreement between diagnostic modalities was assessed using Cohen's kappa (κ) statistic. A p-value of <0.05 was considered statistically significant.

Ethical considerations: The study was approved by the Institutional Ethics Committee prior to initiation. Written informed consent was obtained from all participants or their guardians in the case of minors. Patient confidentiality was maintained throughout the study, and all procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Results

A total of 294 patients with suspected extrapulmonary tuberculosis were included, with a mean age of 36.8 ± 14.2 years. The majority of participants were in the 21–40 years age group (42.9%), followed by 41–60 years (27.9%), while 16.3% were below 20 years and 12.9% were above 60 years. Males constituted 57.1% of the cohort, indicating a male predominance. HIV seropositivity was observed in 11.6% of patients. A previous history of tuberculosis was present in 17.7% of cases, whereas the majority (82.3%) were newly diagnosed (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (n = 294)

Variable	Frequency/mean ± SD	%
Age group (years)		
<20	48	16.3
21–40	126	42.9
41–60	82	27.9
>60	38	12.9
Age (years)	36.8 ± 14.2	—
Gender		
Male	168	57.1
Female	126	42.9
HIV status		
Positive	34	11.6
Negative	260	88.4
Previous TB history		
Yes	52	17.7
No	242	82.3

TB: tuberculosis; HIV: human immunodeficiency virus.

Lymph node aspirates were the most common specimens (35.4%), followed by pleural fluid (24.5%) and ascitic fluid (12.9%). The highest diagnostic yield was observed in pus/abscess samples (69.2%), followed by lymph node aspirates (57.7%). Moderate positivity was seen in synovial fluid (42.9%), whereas lower yields were noted in pleural (33.3%), ascitic (31.6%), CSF (28.6%), and tissue biopsy samples (33.3%). Overall, solid and purulent samples demonstrated higher detection rates compared to serous fluid specimens (Table 2).

Table 2: Distribution of Extrapulmonary Specimens and Diagnostic Yield by Specimen Type (n = 294)

Specimen Type	Frequency	%	Positive	Positivity (%)
Lymph node aspirate	104	35.4	60	57.7
Pleural fluid	72	24.5	24	33.3
Ascitic fluid	38	12.9	12	31.6
CSF	28	9.5	8	28.6
Pus/abscess	26	8.8	18	69.2
Synovial fluid	14	4.8	6	42.9
Tissue biopsy	12	4.1	4	33.3

Positivity (%) denotes detection by GeneXpert MTB/RIF. CSF: cerebrospinal fluid.

Using the composite reference standard, GeneXpert MTB/RIF demonstrated a sensitivity of 87.5% and specificity of 88.3%, with PPV of 82.6% and NPV of 91.2%. Line Probe Assay showed slightly lower sensitivity (81.2%) but higher specificity (93.5%), with PPV of 88.9% and NPV of 88.0%. Thus, GeneXpert exhibited better case detection, while LPA showed greater specificity. When compared with culture, GeneXpert demonstrated a sensitivity of 83.9% and specificity of 85.2%, with PPV of 75.0% and NPV of 90.7%. LPA showed lower sensitivity (78.0%) but higher specificity (92.0%), with PPV of 83.6% and NPV of 88.0%. These findings indicate that GeneXpert is more sensitive in detecting extrapulmonary tuberculosis, whereas LPA is more specific in ruling out disease (Table 3).

Table 3: Diagnostic Performance of Molecular Tests Using Composite Reference Standard (CRS) and Culture (Reference Standard).

Parameter	GeneXpert (%)	LPA (%)
Composite Reference Standard		
Sensitivity	87.5	81.2
Specificity	88.3	93.5
PPV	82.6	88.9
NPV	91.2	88
Culture		
Sensitivity	83.9	78
Specificity	85.2	92
PPV	75	83.6
NPV	90.7	88

CRS includes combined clinical, radiological, and microbiological criteria. PPV: positive predictive value; NPV: negative predictive value.

Rifampicin resistance was identified in 19.6% of isolates by culture-based DST. Comparable resistance rates were observed with GeneXpert (18.8%) and LPA (20.2%). The close similarity across all three modalities indicates strong concordance and supports the utility of molecular tests for rapid detection of rifampicin resistance (Table 4).

Table 4: Detection of Rifampicin Resistance Across Diagnostic Modalities

Modality	Resistant	Sensitive	Total Tested	Resistance
	Frequency			%
Culture DST	22	90	112	19.6
GeneXpert	24	104	128	18.8
LPA	21	83	104	20.2

Culture-based drug susceptibility testing (DST) considered the reference standard. PPV: positive predictive value; NPV: negative predictive value.

Substantial agreement was observed between diagnostic modalities, with κ values of 0.69 for GeneXpert versus culture, 0.74 for LPA versus culture, and 0.71 for GeneXpert versus LPA (all $p < 0.001$). In smear-positive cases (n = 62), both GeneXpert and LPA demonstrated high positivity rates of 93.5% and 90.3%, respectively (Table 5).

Table 5: Agreement of Diagnostic Modalities

Comparison	Kappa (κ)	Interpretation	p-value
GeneXpert vs Culture	0.69	Substantial	<0.001
LPA vs Culture	0.74	Substantial	<0.001
GeneXpert vs LPA	0.71	Substantial	<0.001

DST: drug susceptibility testing; resistance (%) calculated among total tested cases.

Among smear-negative cases (n = 232), GeneXpert showed higher detection (31.9%) compared to LPA (23.3%). Additionally, GeneXpert demonstrated greater positivity in HIV-positive patients (64.7%) compared to HIV-negative individuals (42.3%), whereas LPA showed relatively lower detection in HIV-positive cases (47.1%). These findings highlight the superior performance of GeneXpert in smear-negative and immunocompromised populations (Table 6).

Table 6: Subgroup Analysis of Diagnostic Modalities

Parameters	GeneXpert Positive	LPA Positive
	Frequency (%)	
Smear Status		
Smear positive (n=62)	58 (93.5%)	56 (90.3%)
Smear negative (n=232)	74 (31.9%)	54 (23.3%)
HIV Status		
HIV positive (n=34)	22 (64.7%)	16 (47.1%)
HIV negative (n=260)	110 (42.3%)	102 (39.2%)

κ: Cohen’s kappa coefficient; agreement interpreted as per Landis and Koch classification. HIV: human immunodeficiency virus.

Discussion

The present study evaluated the diagnostic performance of conventional drug susceptibility testing (DST), Line Probe Assay, and GeneXpert MTB/RIF in extrapulmonary tuberculosis (EPTB), a condition known for its diagnostic complexity due to paucibacillary disease and heterogeneous clinical presentation.

The demographic profile of our cohort showed a predominance of younger adults (42.9% in 21–40 years) with a mean age of 36.8 ± 14.2 years and a slight male preponderance (57.1%), which aligns with Indian epidemiological trends reported by Sahukar et al., and Shamseeda et al., where EPTB is more common in economically productive age groups [12,13].

The HIV co-infection rate of 11.6% in our study is comparable to reports from tertiary care settings in India by Jacob et al., and (10–15%), reinforcing the known association between immunosuppression and extrapulmonary disease dissemination [14,15].

In the present study, lymph node aspirates were the most common specimens (35.4%), followed by pleural and ascitic fluids, consistent with earlier Indian studies by Tadesse et al., and Luba et al., which report lymph node TB as the most frequent form of EPTB [16,17]. Notably, the highest diagnostic yield was observed in pus/abscess samples (69.2%) and lymph node aspirates (57.7%), whereas fluid specimens such as CSF (28.6%) and pleural fluid (33.3%) demonstrated lower positivity. This disparity can be explained by the higher bacillary load in solid and purulent specimens compared to serous fluids, which are typically paucibacillary and may contain inhibitory substances affecting molecular amplification [18].

The diagnostic performance analysis revealed that GeneXpert demonstrated superior sensitivity (87.5% using composite reference standard; 83.9% vs culture) compared to LPA (81.2% and 78.0%, respectively), whereas LPA showed higher specificity (93.5% vs CRS; 92.0% vs culture) than GeneXpert. These findings are consistent with studies by Chaudhary et al., and Osei Sekyere et al., which reported GeneXpert sensitivity ranging from 70–90% and specificity above 85% in EPTB, with variable performance depending on specimen type [19,20]. The higher sensitivity of GeneXpert in our study can be attributed to its ability to detect minute quantities of *Mycobacterium tuberculosis* DNA through real-time PCR amplification, even in paucibacillary samples [21]. Conversely, LPA, being a probe-based hybridization assay, requires relatively higher bacillary load or culture amplification, thereby limiting its sensitivity but enhancing specificity [22].

An important finding of this study was the significantly higher detection rate of GeneXpert in smear-negative cases (31.9%) compared to LPA (23.3%), highlighting its added diagnostic value in cases where conventional microscopy fails. This is particularly relevant in EPTB, where smear negativity is common. Similar observations have been reported byChaudhary et al., and Zahoor et al., who demonstrated that GeneXpert substantially improves case detection in smear-negative specimens [23,24]. Additionally, GeneXpert showed higher positivity in HIV-positive patients (64.7%) compared to HIV-negative individuals (42.3%), likely due to higher rates of disseminated disease and bacillary burden in immunocompromised hosts, a finding supported by studies from Yu et al., and Christopher et al., [25,26].

With respect to drug resistance detection, rifampicin resistance rates were comparable across culture DST (19.6%), GeneXpert (18.8%), and LPA (20.2%), demonstrating strong concordance among modalities. The substantial agreement observed ($\kappa = 0.69–0.74$; $p < 0.001$) further validates the reliability of molecular tests for rapid detection of drug resistance. These findings are in agreement with studies by Kohli et al., and Arega et al., which emphasize that molecular assays targeting *rpoB* gene mutations provide accurate and rapid detection of rifampicin resistance, serving as a surrogate marker for multidrug-resistant TB (MDR-TB) [27,28]. Minor discrepancies between phenotypic and genotypic methods can be attributed to silent mutations, heteroresistance, or mutations outside the targeted regions.

Despite the high specificity of LPA, its limited applicability in smear-negative and paucibacillary specimens reduces its standalone utility in EPTB. In contrast, GeneXpert offers a rapid, automated, and highly sensitive diagnostic approach, making it particularly valuable in resource-limited settings with high TB burden [29]. However, its inability to detect resistance beyond rifampicin and potential false positivity due to detection of non-viable bacilli remain limitations. Conventional culture-based DST, although considered the gold standard, is hindered by long turnaround time (up to 6–8 weeks), delaying initiation of appropriate therapy [30].

Limitations

This study has certain limitations. Being a single-center study, the findings may have limited generalizability. The use of a composite reference standard (CRS) may introduce incorporation bias. Line Probe Assay was not performed on all samples, particularly smear-negative cases, which could underestimate its diagnostic performance. Additionally, variability in specimen types and bacillary load may have influenced test sensitivity.

Conclusion

The present study demonstrates that GeneXpert MTB/RIF exhibits superior sensitivity and rapid turnaround time, making it an effective frontline diagnostic tool for extrapulmonary tuberculosis, particularly in smear-negative and HIV-associated cases. Line Probe Assay, although less sensitive, offers higher specificity and reliable detection of drug resistance. Conventional culture-based DST remains essential as a reference standard despite longer processing time. A combined diagnostic approach integrating molecular assays with culture methods can enhance early detection and appropriate management of extrapulmonary tuberculosis, especially in high-burden settings like India.

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