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Comparison of GeneXpert and line probe assay for the detection of *Mycobacterium tuberculosis* in direct sputum samples

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ABSTRACT

Tuberculosis (TB) remains a major global health issue, particularly in low-and-middle-income countries (LMICs) like Indonesia. Diagnostic methods for TB and multidrug-resistant TB (MDR-TB) such as Lowenstein-Jensen (LJ) solid media and Mycobacterium Growth Indicator Tube (MGIT), are time-consuming, causing delays in patient management. Rapid molecular diagnostics, like the GeneXpert MTB/RIF ultra assay and line probe assay (LPA), offer faster and more accurate detection of *Mycobacterium tuberculosis* and drug resistance. This study aimed to compare the efficacy of GeneXpert and LPA in detecting *M. tuberculosis* and assessing drug resistance in sputum samples from 20 patients with confirmed TB. The samples were categorized into four groups based on GeneXpert results: very low, low, medium, and high DNA concentration. GeneXpert identified 20% of samples as rifampicin-resistant, while LPA identified 35%. Additionally, LPA detected isoniazid resistance in 10% of samples. The five discordance results between GeneXpert and LPA, from samples with very low DNA concentrations, were confirmed using MGIT 960 culture DST as the gold standard. The LPA successfully identified 2 (10%) Hr-TB among TB cases detected by the GeneXpert TB/RIF. While LPA demonstrates superior performance characteristics, particularly in detecting isoniazid, GeneXpert demonstrated better sensitivity and specificity, making it a more reliable diagnostic tool under suboptimal conditions, followed by culture-based DST to assure accuracy and examine resistance to other drugs.

Keywords:
GeneXpert;
LPA;
MDR-TB;
Mycobacterium tuberculosis;
tuberculosis

ABSTRACT

Tuberculosis (TB) masih menjadi masalah kesehatan global, terutama di negara berpenghasilan rendah dan menengah seperti Indonesia. Metode diagnostik untuk TB dan TB resistan multi-obat (MDR-TB) seperti media padat Lowenstein-Jensen (LJ) dan Mycobacterium Growth Indicator Tube (MGIT) membutuhkan waktu lama, menyebabkan keterlambatan dalam penanganan pasien. Diagnostik molekuler cepat, seperti GeneXpert MTB/RIF *ultra assay* dan line probe assay (LPA), menawarkan deteksi *Mycobacterium tuberculosis* dan resistansi obat yang lebih cepat dan akurat. Penelitian ini bertujuan untuk membandingkan efektivitas GeneXpert dan LPA dalam mendeteksi *M. tuberculosis* dan menilai resistansi obat pada sampel dahak dari 20 pasien yang terkonfirmasi TB. Sampel dikategorikan dalam empat kelompok berdasarkan konsentrasi DNA yaitu konsentari sanagt rendah, rendah, sedang, dan tinggi. GeneXpert mengidentifikasi 20% sampel sebagai resistan rifampisin, sementara LPA mengidentifikasi 35%. Selain itu, LPA juga mendeteksi resistansi isoniazid pada 10% sampel. Lima hasil discordant antara GeneXpert dan LPA pada sampel dengan konsentrasi DNA rendah dikonfirmasi menggunakan kultur MGIT 960 DST sebagai baku emas. Teknik LPA berhasil mengidentifikasi 2 (10%) Hr-TB di antara kasus TB yang terdeteksi oleh GeneXpert MTB/RIF. Walaupun LPA menunjukkan karakteristik kinerja superior, terutama dalam mendeteksi isoniazid, GeneXpert menunjukkan sensitivitas dan spesifisitas yang lebih baik, menjadikannya alat diagnostik yang lebih andal dalam kondisi suboptimal, diikuti dengan kultur berbasis DST untuk memastikan akurasi dan memeriksa resistansi terhadap obat lainnya.

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INTRODUCTION

Tuberculosis (TB) is a leading global infectious disease, disproportionately affecting low socioeconomic groups, particularly in low-and-middle-income countries (LMICs).[1] Caused by *Mycobacterium tuberculosis*, TB is primarily spread through airborne droplets, posing a significant public health challenge.[2] Indonesia, as a country in Southeast Asia, bears a substantial burden of TB, ranking second globally in TB cases in 2024, according to Indonesia's Ministry of Health. The province of North Sumatra, in particular, ranks fourth in the country for the highest number of TB cases, following West Java, East Java, and Central Java. The rising incidence of multi-drug-resistant tuberculosis (MDR-TB) has further exacerbated the global TB crisis.[3]

In Indonesia, drug susceptibility testing is often performed using Lowenstein-Jensen (LJ) solid media and Mycobacterium Growth Indicator Tube (MGIT). However, these conventional techniques are time-consuming, often taking weeks to yield results, which delays patient management and exacerbates the spread of the disease.[4] Given the urgent need for faster and more accurate diagnostic methods, the GeneXpert MTB/RIF assay and the line probe assay (LPA) have emerged as promising alternatives for the rapid detection of *M. tuberculosis* and drug-resistant TB.

The GeneXpert MTB/RIF assay is an automated, real-time PCR-based test that used to detect *M. tuberculosis* and identify rifampicin resistance.[5] It is widely adopted due to its simplicity, rapid turnaround time, and high sensitivity, even in smear-negative samples. Studies have demonstrated the GeneXpert's excellent performance, with sensitivities ranging from 90.9 to 95.2% and specificities between 97.6 and 100% for respiratory specimens.[6] The ability to quickly detect rifampicin resistance is particularly valuable, as it allows for the prompt initiation of appropriate treatment regimens. The LPA is a molecular diagnostic method that utilizes the reverse hybridization of amplified DNA fragments to specific probes on a strip. This process allows for the simultaneous detection of *M. tuberculosis* and the identification of resistance to various anti-tuberculosis drugs, including rifampicin and isoniazid.[7]

Given the variable results reported in different studies comparing these methods, with some favoring GeneXpert and others showing better performance with LPA, this study aims to provide a comprehensive comparison of the sensitivity and specificity of the GeneXpert MTB/RIF assay and the Line Probe Assay for detecting *M. tuberculosis* and drug-resistant TB in direct sputum samples. By comparing these two rapid molecular techniques, this study seeks to inform better diagnostic practices that could significantly impact TB management, particularly in high-burden regions such as Indonesia.

MATERIAL AND METHODS

Study design, ethics and samples collection

This study was conducted using a prospective cohort design. Sputum samples were collected at the Clinical Microbiology Laboratory of Universitas Sumatera Utara Hospital. The study included 20 *M. tuberculosis* positive samples, confirmed by GeneXpert. These samples were categorized into

four groups based on the GeneXpert results: 5 samples with "very low", 5 with "low", 5 with "moderate", and 5 with "high" DNA concentration. This study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia, under approval number 1094/KEPK/USU/2023.

The GeneXpert MTB/RIF ultra assay

The GeneXpert MTB/RIF Ultra assay involves combining sample treatment reagent with sputum, incubating the mixture for 15 min, transferring the treated sample into a GeneXpert cartridge, and then inserting it into the GeneXpert instrument. The instrument automated the processes of DNA extraction, amplification, and detection, generating a printable test result. The cartridge contained internal controls (lyophilized *Bacillus globigii* spores) and integrates sample processing, PCR amplification, and detection within a single, self-contained.

Line probe assay (LPA)

The LPA used in this study was Genoscholar™. NTM + MDRTB II (Nipro Corporation Limited, Thailand). It was performed on 20 *M. tuberculosis* positive samples identified by GeneXpert. DNA extraction was carried out using the KalGen method. The isolated DNA was then stored at -20°C for subsequent RT-PCR. Amplification was performed using RT-PCR machine and hybridization was performed using the Genoscholar™ NTM + MDRTB II kit. The amplified product was mixed with a denaturation solution and applied to the hybridization strips, which were processed on the MULTIBLOT device for approximately 3 hr. Results were interpreted by observing the line patterns on the strips, indicating the presence of *M. tuberculosis* species, non-tuberculous Mycobacteria, and drug resistance.

The phenotypic drug susceptibility test (pDST)

The phenotypic drug susceptibility test (pDST) was taken as the gold standard for assessing the sensitivity and specificity of the GeneXpert and LPA tests. In cases where there was a discrepancy between the GeneXpert and LPA results, the pDST was conducted to confirm the diagnosis. If the GeneXpert and LPA tests yielded concordant results, it was presumed that the pDST would produce a similar outcome.

Data analysis

Data analysis was done by using R software version (4.3.1) (R Computing, Vienna, Austria). Descriptive statistics for sputum sample sensitive to were presented using frequency and percentage for through tables and ROC curves. The performance of the methods was assessed by calculating sensitivity, specificity, and Cohen's Kappa statistics to measure the concordance between the methods. The sensitivity and specificity of the tests were computed based on overall samples and the different levels of DNA concentration using cycle threshold (CT) including low (> 22 CT), medium (16-22 CT) and high (<16 CT).[8]

Receiver operating characteristics curve (ROC curve)

The ROC curves were used to illustrates the tradeoff between sensitivity and specificity of GeneXpert and LPA against pDST test in predicting a resistant pattern of TB among the samples. The area under curve (AUC) measures the rank correlation between the predicted probabilities of the outcome and the actual observed response. When

the ROC curve approaches the upper left corner of the plot (where sensitivity and specificity both equal 100%), the AUC approaches 100%. An AUC below 70% reflects poor discrimination, whereas values between 80-90% indicate excellent discrimination.[9]

RESULTS

Samples

A total of 20 sputum samples were collected from patients with confirmed tuberculosis. The GeneXpert results classified these samples into 3 groups based on DNA concentration, with ten samples in low category and 5 samples in medium and high categories, respectively (TABLE 1). The overall mean age of the patients was 49.4 yr. Among the 20 patients, 11 (55%) were male, with a mean age of 51.7 yr, and 9 (45%) were female, with a mean age of 46.6 yr.

Molecular diagnosis of TB using LPA

In this study, the LPA successfully identified *M. tuberculosis* in all 20 (100%) sputum samples collected from patients with confirmed tuberculosis. This demonstrates the high sensitivity and reliability of LPA in TB molecular diagnosis.

TABLE 1. Patient characteristics

Subject	Age (yr)	Gender	GeneXpert		Duration of TB treatment (yr)
			Resistance profile	Bacterial load	
1	68	F	RIF-R	Low	< 5
2	49	M	RIF-S	High	< 5
3	27	F	RIF-S	High	< 5
4	49	M	RIF-S	Low	< 5
5	18	M	RIF-S	Very Low	< 5
6	88	M	RIF-S	Very Low	< 5
7	30	F	RIF-S	Very Low	< 5
8	62	F	RIF-S	Medium	< 5
9	74	F	RIF-S	Low	< 5
10	32	M	RIF-S	High	< 5
11	49	M	RIF-S	Medium	< 5
12	55	M	RIF-S	Low	< 5
13	60	M	RIF-S	Very Low	< 5
14	63	F	RIF-S	Medium	< 5
15	46	M	RIF-S	High	< 5
16	27	F	RIF-S	Medium	< 5
17	72	M	RIF-S	Low	< 5
18	44	F	RIF-R	Medium	< 5
19	51	M	RIF-R	High	< 5
20	24	F	RIF-R	Very Low	< 5

Drug susceptibility pattern of GeneXpert and LPA

TABLE 2 presents the percentage of direct sputum sample resistant to anti tuberculosis drugs using GeneXpert and LPA. GeneXpert identified 20% rifampicin resistant and 80% sensitive, while LPA detected 35% rifampicin resistant and 65% sensitive. LPA also provided isoniazid resistance information, with 10% resistance and 90% sensitive. The absence of INH sensitivity results from GeneXpert is due to the nature of the test, as the standard GeneXpert MTB/RIF assay only detects rifampicin resistance and does not assess isoniazid susceptibility. These findings highlight LPA's importance in offering a comprehensive drug resistance profile for tailoring effective treatment regimens for MDR-TB patients. The LPA results (FIGURE 1) showed various resistance patterns, including rifampicin and isoniazid sensitivity, and cases of resistance to one or both drugs, demonstrating different profiles of drug resistance in *M. tuberculosis*.

TABLE 2. Percentage of direct sputum sample resistant to anti-tuberculosis drugs (OAT) using GeneXpert and LPA (n=20).

Type of the test	Anti-tuberculosis drug sensitivity [n (%)]			
	Rifampicin		Isoniazid	
	Resistant	Sensitive	Resistant	Sensitive
GeneXpert	4 (20)	16 (80)	N/A	N/A
LPA	7 (35)	13 (65)	2 (10)	18 (90)

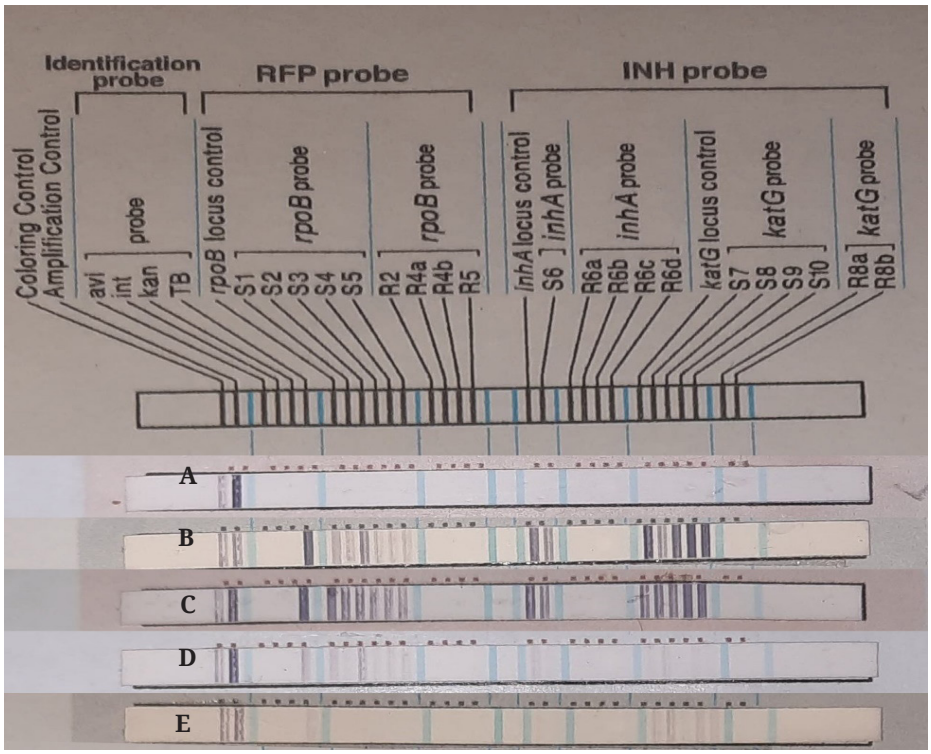

FIGURE 1. Line probe assay (LPA) results: (A) Negative control; (B) Positive control with other NTM; (C) sample detected M. *tuberculosis* with rifampicin sensitive and isoniazid sensitive; (D) sample detected *M. tuberculosis* with rifampicin sensitive and isoniazid resistant; (E) sample detected *M. tuberculosis* with rifampicin resistant and isoniazid sensitive.

The performance of GeneXpert and LPA in detecting rifampicin resistance is compared in TABLE 2. Both tests showed 100% sensitivity in overall and in all levels of DNA concentration. However, there is higher rate of false positive in low concentration of DNA in both GeneXpert and LPA, resulting in lower specificity. The specificity to identify absence of rifampicin resistance was 56% in LPA and 89% in GeneXpert. Several studies have noted that the sensitivity and specificity of GeneXpert declines in samples with lower bacterial concentrations. This issue has been highlighted in cases where discordant results between GeneXpert and other diagnostic methods, such as LPA or DST culture, occur due to very low bacterial presence.[10,11]

FIGURE 2a and 2c highlighted in overall samples, AUC for predicting rifampicin resistance was 87.5% for GeneXpert, compared to 71.4% for the LPA. This suggests that GeneXpert demonstrates superior diagnostic accuracy under standard conditions. In FIGURE 2b and 2d, the AUCs of both GeneXpert and LPA shows 100%, when medium and high DNA concentrations of sputum were used, highlighting their effectiveness in detecting rifampicin resistance with sufficient sample quality. However, in samples with low DNA concentrations, the AUC dropped significantly, with GeneXpert achieving 75% and LPA only 60%. These findings indicate that while both methods are highly effective with optimal DNA concentrations, GeneXpert maintains better sensitivity and specificity under suboptimal conditions.

TABLE 3. Performance of GeneXpert and LPA test in detecting of rifampicin resistance

Variable	pDST					
	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)
GeneXpert						
Overall	3	0	1	16	100 (29–100)	94 (71–100)
DNA concentration						
• Low	1	0	1	8	100 (2–100)	89 (52–100)
• Medium	1	0	0	4	100 (2–100)	100 (40–100)
• High	1	0	0	4	100 (2–100)	100 (40–100)
LPA						
Overall	3	0	4	13	100 (29–100)	76 (50–93)
DNA concentration						
• Low	1	0	4	5	100 (29–100)	56 (21–86)
• Medium	1	0	0	4	100 (29–100)	100 (40– 100)
• High	1	0	0	4	100% (29–100%)	100 (40–100)

TP=True positive; FN=False negative; FP=False positive; TN=True negative

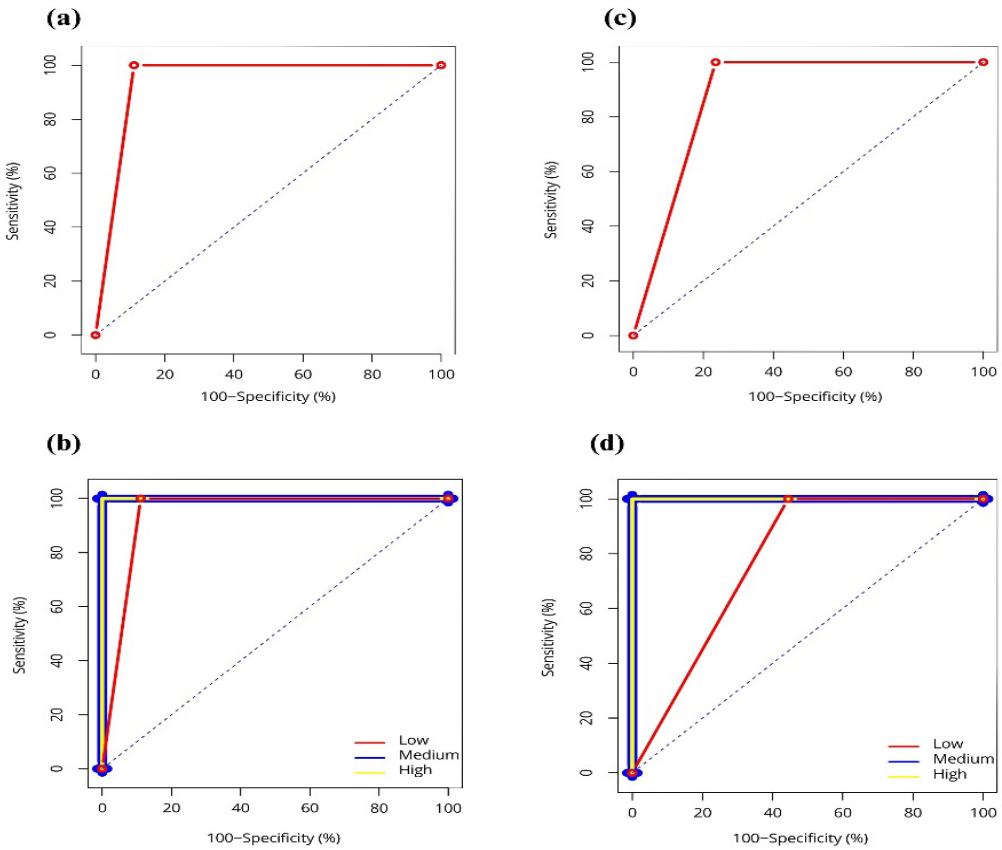

FIGURE 2. ROC curves illustrating performances of a) overall GeneXpert; b) GeneXpert with different DNA concentration; c) overall LPA; and d) LPA test with different DNA concentration in detecting Rifampicin resistance using pDST as the gold standard.

TABLE 4. Comparison of INH resistance between LPA and pDST using low DNA concentration of sputum samples (including "Not evaluated" cases).

LPA	pDST			Kappa
	Sensitive	Resistance	Not evaluated	
Sensitive	2	2	0	
Resistant	0	1	0	0.67
Not evaluated	0	0	4	

TABLE 5. Comparison of INH resistance between LPA and pDST using low DNA concentration of sputum samples (excluding "Not evaluated" cases).

LPA	pDST		Kappa
	Sensitive	Resistance	
Sensitive	2	2	
Resistant	0	1	0.29
Not evaluated	0	0	

TABLE 4 presents the comparison of INH resistance between the LPA and pDST using sputum samples with low DNA concentrations, including those categorized as “not evaluated”. The initial analysis showed moderate agreement (Kappa = 0.67). However, a sensitivity analysis was performed by excluding the “not evaluated” samples, as shown in TABLE 5, which resulted in a significantly lower Kappa value (0.29), indicating poor agreement. This suggests that the inclusion of “not evaluated” samples may have overestimated the concordance between LPA and pDST. The findings highlight notable discrepancies, particularly when using samples with low DNA concentrations, which may affect the reliability of LPA in detecting INH resistance in such cases.

DISCUSSION

The comparison between GeneXpert and LPA in detecting rifampicin resistance reveals that both methods perform effectively with medium and high DNA concentrations, achieving 100% AUC. However, under low DNA concentration conditions, GeneXpert demonstrates superior sensitivity with an AUC of 75%, compared to LPA’s 60%, indicating better performance under suboptimal conditions. Despite the high accuracy overall, the specificity of rifampicin resistance detection is notably higher in GeneXpert (89%) compared to LPA (56%), particularly in low-concentration samples, where false positives are more common. The poor agreement (Kappa =0.29) between the two methods underscores the importance of confirmatory testing, especially in discordant cases.

The presence of discordant rifampicin resistance is associated with GeneXpert probe B, showing a delay in probe binding compared to probe dropout and delays G4 cartridge between probe binding delays (ΔCt) 4–4.9. Berhanu *et al.*,[10] study found that 22 out of 263 subjects exhibited discordance in rifampicin resistance, specifically associated with GeneXpert probe B and related to probe binding delays rather than probe dropout. The ΔCt observed ranged from 4 to 4.9. Another study conducted in Republic of Haiti indicated that similar discordances may arise from variations in probe performance under different conditions, emphasizing the importance of careful interpretation of GeneXpert results.[12]

Line probe assays are designed to detect key resistance mutations for both first-line and second-line TB drugs. The LPAs can also identify both wild-type and resistance mutations in a single patient, known as heteroresistance.[13] LPAs signal heteroresistance by detecting both wild-type and specific mutations in the *rpoB* gene. Unlike LPAs, GeneXpert mainly detects resistance at higher mutation levels, making it more likely to show rifampicin susceptibility when heteroresistance is present.[14]

Line probe assays demonstrates superior performance characteristics, particularly in detecting isoniazid. These findings emphasize the potential limitations of molecular assays and the necessity of confirmatory testing. Given Indonesia’s high tuberculosis burden, integrating GeneXpert with additional DST analysis is essential for improving diagnostic accuracy and patient management.

The use of direct sputum samples in this study ensures the evaluation reflects real-world clinical conditions. Additionally, the statistical analysis provides a detailed comparison of GeneXpert and LPAs, highlighting their respective strengths and limitations. However, the relatively small sample size may limit the generalizability of the findings, and the lack of pDST evaluation for all samples could affect the robustness of some conclusions.

From a clinical perspective, GeneXpert’s higher sensitivity in low-DNA samples suggests its potential

utility for early detection, particularly in challenging conditions where sample quality is suboptimal. However, the lower specificity of LPAs in these conditions underscores the need for confirmatory testing, especially in discordant results and suspected heteroresistance cases. Integrating GeneXpert with additional DST methods could enhance diagnostic accuracy and improve TB management strategies in Indonesia.

CONCLUSION

In conclusion, both GeneXpert and LPA are effective methods for detecting rifampicin resistance, particularly at medium and high DNA concentrations, where their diagnostic accuracy is 100%. However, GeneXpert shows superior sensitivity and specificity in samples with low DNA concentrations. The moderate agreement between the two methods highlights the need for confirmatory testing in discordant cases. The WHO recommended the GeneXpert MTB/RIF Ultra as rapid molecular diagnosis in 2017,[15] confirming that the cartridges yield non-inferiority results to traditional methods.

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