

**GENEXPERT - IS IT AN EXPERT IN DIAGNOSIS OF EXTRAPULMONARY TUBERCULOSIS?***Mitali Mukund Nayak<sup>1</sup>, Himanshu Suresh Thakker<sup>2</sup>, Ruhee Gotmare<sup>3</sup>*<sup>1</sup>*Professor and HOD, Department of Pulmonary Medicine, Terna Medical College, Nerul.*<sup>2</sup>*Senior Resident, Department of Pulmonary Medicine, Terna Medical College, Nerul.*<sup>3</sup>*Junior Resident, Department of Pulmonary Medicine, Terna Medical College, Nerul.***ABSTRACT****BACKGROUND**

Six countries in Asia account for 60% of the total new tuberculosis cases occurring globally with India leading the count. India accounts for approximately 25% of global incidence of tuberculosis with almost 2 deaths every 3 minutes due to tuberculosis alone. GeneXpert is a comparatively newer diagnostic test for detecting Mycobacterium tuberculosis complex, which uses the PCR to test specimens and simultaneously detects resistance to rifampicin, thus allowing diagnosis of DR-TB within a couple of hours.

The present study was conducted to find the sensitivity and specificity of GeneXpert in extrapulmonary samples (lymph node and pleural fluid) and compare the results with those of smear and AFB culture with an aim to provide rapid diagnostic test to patients with suspected extrapulmonary tuberculosis.

**MATERIALS AND METHODS**

A retrospective data analysis of reports of extrapulmonary samples (lymph node and pleural fluid) of 45 patients sent for AFB smear, GeneXpert and AFB culture during routine investigations were studied.

**RESULTS**

Sensitivity of GeneXpert in lymph node samples was found to be 94.12% and specificity was 30.77% with positive predictive value of 64% and negative predictive value of 80%. The sensitivity of GeneXpert in pleural fluid samples was found to be 60% with 100% specificity. The positive predictive value was 100% and negative predictive value was 83.33%.

**CONCLUSION**

The overall sensitivity of GeneXpert was 96.67% with specificity of 100%, positive predictive value of 100% and negative predictive value of 83.33%. Thus, it is a valuable test for diagnosing extrapulmonary tuberculosis at the earliest with an added advantage of detecting resistance for rifampicin.

**KEYWORDS**

GeneXpert, Extrapulmonary Tuberculosis, AFB Culture, Sputum Smear Microscopy.

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**BACKGROUND**

In 2015, 10.4 million people were diagnosed with tuberculosis and 1.8 million people died from tuberculosis, while 95% of TB deaths occurred in low and middle income countries.<sup>1</sup> According to WHO reports in 2015, the largest number of new TB cases occurred in Asia with 61% new cases. Six countries in Asia account for 60% of the total with India leading the count.<sup>1</sup> India accounts for approximately 25% of global incidence of tuberculosis with almost 2 deaths every 3 minutes due to tuberculosis alone. The rapid diagnosis of tuberculosis is of primary importance to ensure availability of prompt treatment to the patient as well as

control of tuberculosis in the community. GeneXpert is a comparatively newer diagnostic test for detecting MTB complex, which uses the PCR to test specimens and simultaneously detects resistance to rifampicin, thus allowing diagnosis of DR-TB within a couple of hours. The present study was conducted to find the sensitivity and specificity of GeneXpert in extrapulmonary samples (lymph node and pleural fluid) and compare the results with those of smear and AFB culture with an aim to provide rapid diagnostic test to all TB patients.

TB is preventable and completely curable yet about 7,10,000 people died of TB in 2015. Incomplete treatment can lead to drug resistant TB. Over 2,00,000 people got DR-TB in 2015. TB is the largest killer among communicable diseases in the 15 to 49 age group when humans are most productive. Over half of these were among men (5.9 million) and women constituted over a third (3.5 million). Of these India (23%) and Indonesia (10%) alone account for a third of the world's burden. Though India appears to be the major source for the region's TB numbers, it actually ranks number six in terms of incidence rate. In SEA, estimated incidence

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of MDR/RR-TB was 2,00,000 with India alone accounting for 1,30,000.

Some persistent barriers to TB control in the SEA region include-<sup>2</sup>

1. Absence of universal health coverage as well as limited access to quality health services and fully subsidised treatment for chronic diseases.
2. Widespread shortage and uneven distribution of well-trained, well-equipped and motivated health workers.
3. Insufficient data collection capacity leading to gross neglect of TB monitoring and underreporting of incidence.
4. Failure to address poverty under nutrition and risk factors that adversely influence exposure to tuberculosis.
5. Insufficient strategies to address populations at risk including targeted screening and investigation.
6. Lack of regulatory systems and weak accountability mechanisms as well as poor governance in public health management.
7. Insufficient long-term strategies to address the socioeconomic factors that germinate tuberculosis - poverty reduction, better nutrition, better living and work conditions as well as strategies to mitigate the impact of migration.
8. Above all, there is an overreliance on donors and insufficient resource mobilisation even in countries with small funding gaps. National governments average just 41% of current budgets for NTPs.

**Aims and Objectives**

This study was carried out with the aim of determining sensitivity and specificity of GeneXpert for detection of tuberculosis in extrapulmonary specimens and comparing it with both smear and TB cultures to determine if all the extrapulmonary samples should be subjected to GeneXpert in order to improve the diagnostic yield and simultaneously provide early diagnosis of drug resistance if any.

**MATERIALS AND METHODS**

A retrospective data analysis of reports of extrapulmonary samples (lymph node and pleural fluid) of 45 patients sent for AFB smear, GeneXpert and AFB culture during routine investigations were studied. The study included all patients diagnosed as pleural or lymph node tuberculosis on the basis of clinicroadiological or microbiological findings.

**RESULTS**

Out of 30 lymph node samples studied, AFB smear was found positive only in 2 specimens and both of these were culture and GeneXpert positive. Out of the 28 smear negative, 15 were culture positive, out of which 14 were also GeneXpert positive. Out of the 13 culture negative samples, 9 were found to be positive on GeneXpert. Sensitivity of GeneXpert in lymph node samples was found to be 94.12% and specificity was 30.77 with positive predictive value of 64% and negative predictive value of 80%.

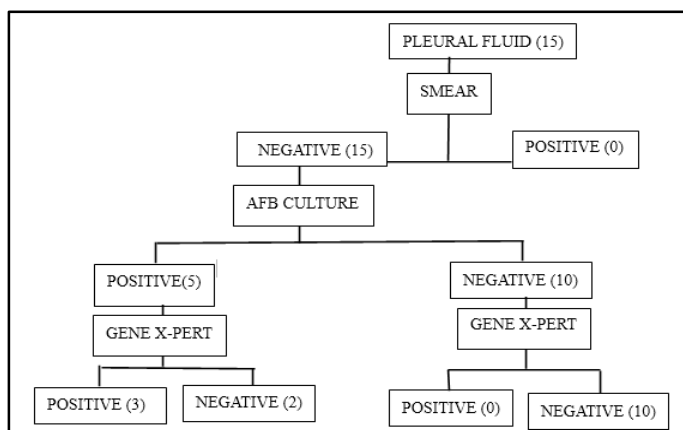
Lymph Node (30)				
		AFB		Total
		Positive	Negative	
GeneXpert	Positive	16	9	25
	Negative	1	4	5
	<b>Total</b>	<b>17</b>	<b>13</b>	<b>30</b>
Sensitivity				94.12%
Specificity				30.77%
Positive predictive value				64%
Negative predictive value				80%

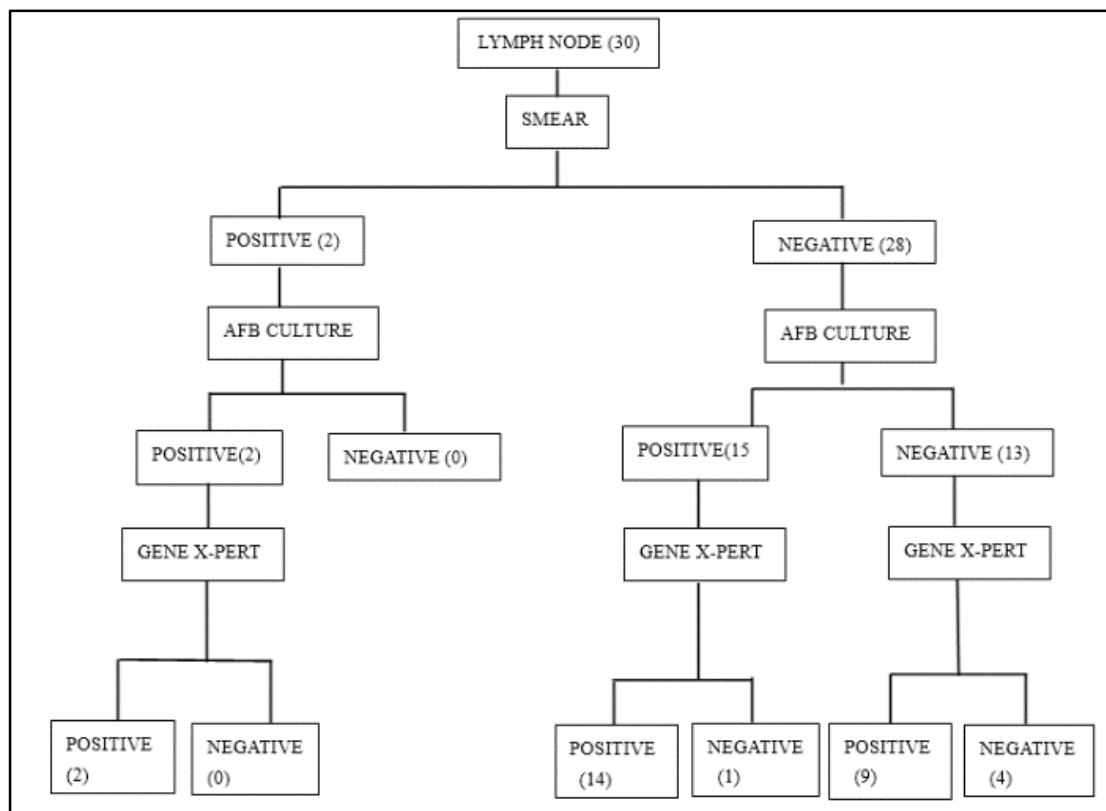
*Table 1.*

Pleural Fluid Smear Negative				
		AFB		Total
		Positive	Negative	
GeneXpert	Positive	3	0	3
	Negative	2	10	12
	<b>Total</b>	<b>5</b>	<b>10</b>	<b>15</b>
Sensitivity				60%
Specificity				100%
Positive predictive value				100%
Negative predictive value				83.33%

*Table 2.*

All 15 pleural fluid samples were smear negative. Only 5 pleural fluid samples were found to be culture positive, out of which 3 were GeneXpert positive. All the 10 AFB culture negative samples were also GeneXpert negative. The sensitivity of GeneXpert in pleural fluid samples was found to be 60% with 100% specificity. The positive predictive value was 100% and negative predictive value was 83.33%.





**DISCUSSION**

According to WHO report 2015, the incidence of tuberculosis in India alone is 2.2 million cases per year out of an estimated 9.6 million new cases detected globally, which is approximately 1/4<sup>th</sup> of the global burden. Extrapulmonary epidemiological data suggests that extrapulmonary tuberculosis constitutes of about 15-20% of all TB cases, but among HIV-TB coinfection it accounts for 50% of cases.<sup>3</sup> Out of 1,183,373 new TB cases notified globally, 2,34,029 (20%) were reported to be cases of extrapulmonary tuberculosis.<sup>4</sup> Difficulty in sampling from extrapulmonary tuberculosis sites and paucibacillary nature of specimens make extrapulmonary tuberculosis a diagnostic challenge. Although, smear examination is a comparatively easily performed test involving less expenditure. The sensitivity of smear microscopy in extrapulmonary specimens is low.<sup>5</sup> Mycobacterium tuberculosis culture is a time consuming process with a turnaround time of 6-8 weeks requiring trained personnel and a well-equipped laboratory. This may lead to a delayed diagnosis leading to delay in initiation of anti-TB treatment and also results in spread of the disease in the community. GeneXpert is a fully automated commercially available rapid diagnostic test using PCR to test genetic material specific to mycobacterium tuberculosis and simultaneously detect a gene that most commonly confers resistance to rifampicin - the rpoB gene. Originally designed to test sputum samples in patient of active tuberculosis, this test has been shown to perform less well in paucibacillary disease as many forms of extrapulmonary tuberculosis require invasive sampling methods. The size and quality of specimens may affect the sensitivity of the test.<sup>5</sup> However, WHO strongly recommended the use of Xpert, MTB/RIF as an additional test to conventional smear

microscopy, culture and cytology in FNAC specimens for diagnosis of lymph node tuberculosis.<sup>5</sup> In a study performed by Armand et al, the sensitivity of test for smear positive and smear negative extrapulmonary samples have been reported to be 100% and 37%.<sup>6</sup> In a study by Zeka et al, sensitivity was found to be 100% for smear positive extrapulmonary specimens, which was similar to previous study, however, study revealed 63% specificity for smear-negative specimens.<sup>7</sup> In a study by Narute et al, the Xpert helped to diagnose 58% of smear negative extrapulmonary specimens.<sup>8</sup> In our study, sensitivity of GeneXpert in lymph node samples was found to be 94.12% and specificity was 30.77% with positive predictive value of 64% and negative predictive value of 80% and sensitivity of GeneXpert in pleural fluid samples was found to be 60% with 100% specificity. The positive predictive value was 100% and negative predictive value was 83.33%. The sensitivity and specificity of GeneXpert in smear positive extrapulmonary specimens was 96.67% and 33%, respectively with positive predictive value of 93.54% and negative predictive value of 50%, which was in accordance with previous studies. In smear-negative specimens, the sensitivity and specificity was found to be 63.63% and 100%, respectively with positive predictive value of 100% and negative predictive value of 38.46%. In our study, the sensitivity of GeneXpert in smear-negative specimens was found to be higher as compared to previous studies. The overall sensitivity of GeneXpert was 96.67% with specificity of 100%, positive predictive value of 100% and negative predictive value of 83.33%. In a study conducted by S.K. Sharma et al study, it was observed that the Xpert assay detected 71% of the "confirmed TB" cases where culture and response to anti-TB treatment were positive. It also identified 68% of "possible

TB" cases where culture, biochemical and histopathology reports were negative and only the response to anti-TB treatment was positive.<sup>9</sup> Of the cases where all parameters were negative, Xpert MTB/RIF detected 0.8% of these cases as positive. High specificity of the assay in all the specimens explains the low false positivity achieved by this diagnostic tool, which can thus be a useful rule-in test for extrapulmonary TB diagnosis.<sup>9</sup>

### CONCLUSION

GeneXpert is a fully automated commercially available rapid diagnostic test using PCR to test genetic material specific to mycobacterium tuberculosis and simultaneously detect a gene that most commonly confers resistance to rifampicin - the *rpoB* gene. In our study, sensitivity of GeneXpert in lymph node samples was found to be 94.12% and specificity was 30.77 with positive predictive value of 64% and negative predictive value of 80%. The sensitivity of GeneXpert in pleural fluid samples was found to be 60% with 100% specificity. The positive predictive value was 100% and negative predictive value was 83.33%. The sensitivity and specificity of GeneXpert in smear positive extrapulmonary specimens was 96.67% and 33% respectively with positive predictive value of 93.54% and negative predictive value of 50%, which was in accordance with previous studies. In smear-negative specimens, the sensitivity and specificity was found to be 63.63% and 100%, respectively with positive predictive value of 100% and negative predictive value of 38.46%. In our study, the sensitivity of GeneXpert in smear-negative specimens was found to be higher as compared to previous studies. The overall sensitivity of GeneXpert was 96.67% with specificity of 100%, positive predictive value of 100% and negative predictive value of 83.33%. Thus, it is a valuable supplementary test for diagnosing extrapulmonary

tuberculosis at the earliest with an added advantage of detecting resistance for rifampicin.

### REFERENCES

- [1] WHO media center tuberculosis fact sheet reviewed 2017.
- [2] WHO bending the curve ending TB 2030-Annual report 2017.
- [3] Sharma SK, Mohan A. Extrapulmonary tuberculosis. *Indian J Med Res* 2004;120(4):316-353.
- [4] Global tuberculosis report 2013. Geneva: World Health Organization 2013.
- [5] Index TB Guidelines. Recommendations for the use of X-pert MTB/RIF in extrapulmonary TB diagnosis. WHO 2016.
- [6] Armand S, Vanhuls P, Delcroix G, et al. Comparison of the Xpert MTB/RIF test with an IS6110-TaqMan real-time PCR assay for direct detection of Mycobacterium tuberculosis in respiratory and non-respiratory specimens. *J Clin Microbiol* 2011;49(5):1772-1776.
- [7] Zeka AN, Tasbakan S, Cavusoglu C. Evaluation of the geneX-pert MTB/RIF assay for rapid diagnosis of tuberculosis and detection of rifampicin resistance in pulmonary and extrapulmonary specimens. *J Clin Microbiol* 2011;49(12):4138-4141.
- [8] Narute S, Salgia K, Singhal P, et al. Comparative study of gene Xpert MTB/RIF, smear microscopy and TB MGIT culture in diagnosis of tuberculosis in India. *European Respiratory Journal* 2015;46:PA1533.
- [9] Sharma SK, Kohli M, Chaubey J, et al. Evaluation of Xpert MTB/RIF assay performance in diagnosing extrapulmonary tuberculosis among adults in a tertiary care centre in India. *Eur Respir J* 2014;44(4):1090-1093.