Hong Kong Tuberculosis, Chest and Heart Diseases Association
Scientific Committee on Lung Health
Final report – Completion form

Important: Please submit the original copy and an electronic version of the Final Report and any attachments. Complete all sections with sufficient detail to allow review of the findings and effectiveness of the project. Incomplete or insufficiently detailed reports will be returned for revision and resubmission. The principal applicant is required to sign the Completion form.

1. **Project No.:** TB project 2/2014

2. **Grant Period:** Commencement Date: December 2014 End Date: June 2017

3. **Title of Project:**
Application on GeneXpert on bronchoscopic samples in the clinical management of patients suspicious of Tuberculosis

4. **Principal Applicant:**
Dr. TO Kin Wang

5. **Administering Institution:**
Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong

6. **Aims/ Objectives of the research:** List the main objectives as stated in the approved proposal.

Approved aims/ objectives	Objectives / indicators achieved Low 1 2 3 4 High 5
To answer the following clinical questions: 1. How is the performance of the GeneXpert MTB/RIF test in intermediate likelihood of cases suspected of TB ? Will GeneXpert in BAL for sputum PCR negative samples provided extra diagnostic benefit? 2. Could these results generate robust guidelines on the clinical application of GeneXpert MTB/RIF based on the pretest probability?	5 : GeneXpert facilitate the diagnosis and treatment in suspicious cases which otherwise have to wait for longer time. 4: GeneXpert can be recommended as an additional test to facilitate the diagnosis

7. **Timetable of Work:** Document the study progress according to the proposed timetable.

- 1st to 5th month: planning (July to November 2014)
- 6th month to 18th month (December 2014 to December 2015): patient recruitment, obtaining BAL samples
- 19th month (January 2016): initial planning for finishing patient recruitment in this month. However, only ~ 50% of the proposed 219 samples were collected. Therefore patient recruitment continued. Review of all available results, patient follow up and record monitoring continued.
- 33rd month (March 2017): End of patient recruitment as 227 samples were collected (over target numbers of 219 samples). Original plan of finishing follow up patients but since recruitment process was continued till this time point, follow up for the patients was continued. Data analysis started.
- 36th month (June 2017): Final data analysis finished.

8. **Summary of the project and its results in 300 words:**

Background: There is limited experience on clinical use of GeneXpert on bronchoalveolar lavage (BAL) fluid samples obtained from patients clinically suspected of pulmonary tuberculosis (TB) in intermediate burden settings.

Methods: sputum acid-fast-bacilli (AFB) smear negative patients were offered bronchoscopy. BAL fluid was collected for AFB smear, TB culture, Cobas Taqman TB polymerase chain reaction (PCR) and for GeneXpert. Cases were diagnosed as TB if any one of the tests was positive.

Results: From December 2014 to February 2017, 227 samples were collected. Patients' mean(SD) age was 60.7(15) years, 143 were males and 84 were females. Cough and haemoptysis were the presenting symptoms in 70% and 37.4% respectively. Apical shadows in chest X-ray (CXR) and apical cavitations in computed tomography (CT) were more common in GeneXpert positive cases (p=0.01 and 0.02 respectively). Sensitivities and specificity of GeneXpert was 80% and 98% respectively. The positive predictive value and negative predictive value was 92.3 and 95.1% respectively. There were 9 false negative GeneXpert samples (8 were Cobas Taqman TB PCR negative): 6 were diagnosed by BAL culture, 2 by biopsy and one by Cobas Taqman TB PCR. There were 3 false positive cases with negative culture, 2 were put on empirical treatment with favorable clinical responses, while one defaulted follow up.

Conclusion: GeneXpert in BAL samples has high specificity and similar performance as Cobas Taqman PCR to rule in TB for initiating early treatment in clinical suspicious cases. However, it cannot replace other investigations as the only test for diagnosing pulmonary TB.

9. **Final report (to be submitted on or before 30 September 2017 with an attachment)**
10. **Budget & expenditure (to be provided by The Chinese University of Hong Kong)**

	To Kin Wang	31/8/2017
Signature of principal applicant	**Name**	**Date**

Final Report

See the details in Application Form on p.10-12

Project Title:

Application of GeneXpert on bronchoalveolar lavage samples in the clinical management of patients suspicious of tuberculosis in an intermediate-burden setting

Reference number: TB project 2/2014

Investigators :

Dr. To Kin Wang[a]

Professor Kam Kai Man[b]

Professor Lee Shui Shan[b]

Professor Denise Chan, Research Assistant Professor[b]

[a]Respiratory Division, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong

[b]Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong.

Administering Institution: Stanley Ho Centre for Emerging Infectious Diseases, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong.

Date of Submission: 9/2017

Summary

Background: There is limited experience on clinical use of GeneXpert on bronchoalveolar lavage (BAL) fluid samples obtained from patients clinically suspected of pulmonary tuberculosis (TB) in intermediate burden settings.

Methods: sputum acid-fast-bacilli (AFB) smear negative patients were offered bronchoscopy. BAL fluid was collected for AFB smear, TB culture, Cobas Taqman TB polymerase chain reaction (PCR) and for GeneXpert. Cases were diagnosed as TB if any one of the tests was positive.

Results: From December 2014 to February 2017, 227 samples were collected. Patients' mean(SD) age was 60.7(15) years, 143 were males and 84 were females. Cough and haemoptysis were the presenting symptoms in 70% and 37.4% respectively. Apical shadows in chest X-ray (CXR) and apical cavitations in computed tomography (CT) were more common in GeneXpert positive cases (p=0.01 and 0.02 respectively). Sensitivities and specificity of GeneXpert was 80% and 98% respectively. The positive predictive value and negative predictive value was 92.3 and 95.1% respectively. There were 9 false negative GeneXpert samples (8 were Cobas Taqman TB PCR negative): 6 were diagnosed by BAL culture, 2 by biopsy and one by Cobas Taqman TB PCR. There were 3 false positive cases with negative culture, 2 were put on empirical treatment with favorable clinical responses, while one defaulted follow up.

Conclusion: GeneXpert in BAL samples has high specificity and similar performance as Cobas Taqman PCR to rule in TB for initiating early treatment in clinical suspicious cases. However, it cannot replace other investigations as the only test for diagnosing pulmonary TB.

Background

Tuberculosis (TB) is an ancient disease which co-existed with humans for millennia and still poses a major health problem in modern days. In 2015, the World Health Organization (WHO) estimated that the global incidence of TB was 10.4 million.[1] Early diagnosis of TB is a critical step for TB control. Sputum smear microscopy for acid-fast bacilli (AFB) remains an important initial step for diagnosis for more than a century but the sensitivity can vary from 20-80% depending on the mycobacterial load, as well as performance of microscopist.[2] Culture of mycobacteria is the conventional gold standard of diagnosis with higher sensitivity and specificity of over 80% and 99% respectively; but it takes weeks for results even with liquid culture methods.[3] GeneXpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) is a fully automated nucleic acid amplification (NAAT) system which has been endorsed by the WHO since 2010 for rapid diagnosis of TB using sputum and certain non-respiratory samples. Specifically, it enables diagnosis to be made within few hours after sample collection.[1]

In patients suspected of TB but unable to produce sputum, the confirmation of diagnosis can become very challenging. Although the WHO recommends GeneXpert as part of the assessment in smear negative sputum,[4] the sensitivity of GeneXpert on smear negative sputum sample was suboptimal. The reported values of sensitivity on smear negative sputum samples ranged from 48% to 75%.[5-7] Bronchoscopy with bronchoalveolar lavage (BAL) is commonly offered in tertiary referral centers in an effort to provide further samples for diagnosis. There is presently scanty data on the utilization of GeneXpert with BAL samples. Many studies on GeneXpert were either retrospectively conducted in low-burden areas in which the incidence rate is less than 10 cases per 100,000 population per year, or in few high-burden countries which contribute around 85% of the global burden, e.g. South Africa. There is limited prospective data from intermediate-burden areas. In recent years, TB incidence continued to decline in some high-burden countries, such that they progress to a lower incidence (intermediate burden) and, at the same time, increased country resource for diagnostics. It is important that an assessment of use of GeneXpert be made in such settings, so that these countries can plan for future of their TB programs.

Aims and Objectives

We aim to study prospectively the role of GeneXpert in Hong Kong in which the incidence of TB in 2015 was 71 per 100000 population,[8] an intermediate TB burden area. Use of GeneXpert is still not a universal practice in Hong Kong. It would take a few days for the results of smear microscopy, conventional PCR test and several weeks for culture of the BAL to be available. This study investigated the role of GeneXpert facilitating the diagnosis of TB using bronchoscopic samples in patients with negative smear sputum.

Methods

The study was conducted at the Department of Medicine and Therapeutics, Prince of Wales Hospital in Hong Kong between December 2014 to February 2017. Patients who were clinically suspected of pulmonary TB, but who could not produce sputum or were sputum AFB-smear negative, were seen by pulmonologist for assessment of further management. Patients who were offered bronchoscopy as the next step of investigation were recruited into the study after signing an informed consent. Bronchoscopy was performed by respiratory specialists and BAL samples were collected under local anesthesia following the usual clinical practice. The tip of the bronchoscope was advanced to a site closest to the location that corresponded to the radiological abnormality on computed tomography of thorax (CT-thorax) or CXR, and was wedged at that position. Up to approximately 100mL of normal saline (0.9% NaCl) was instilled at the site to ensure adequate return for AFB smear, TB culture and Cobas Taqman TB-PCR. An extra 5 mL of BAL fluid was collected for GeneXpert, of which 1.5ml was transferred to the GeneXpert cartridge for subsequent analysis according to the manufacturer's instructions. Attending clinician would then decide if anti-TB treatment was to be started after bronchoscopy, and patients were subsequently followed up. Sensitivity, specificity, positive and negative predictive values were calculated accordingly. Statistical analysis was performed using IBM SPSS Statistics 20 (IBM, NY, USA). A two-sided p-value of ≤ 0.05 was taken as indicative of statistical significance.

Diagnosis of pulmonary TB

A clinical diagnosis of TB was made if either BAL smear, BAL TB PCR or GeneXpert was positive, or if biopsy results were available and clinical picture suggestive of TB. Attending physicians then decided if anti-TB treatment would be started based on the overall clinical presentation. A definite diagnosis of TB was made when BAL TB culture was positive. Patients were classified as non-TB if none of the investigations was positive, but clinicians could start empirical anti-TB treatment if warranted by high clinical suspicion of active TB.

Project Progress, timeline, results presentation

1st to 5th month: planning (July to November 2014)

6th month to 18th month (December 2014 to December 2015): patient recruitment, obtaining BAL samples

19th month (January 2016): initial planning for finishing patient recruitment in this month. However, only ~ 50% of the proposed 219 samples were collected. Therefore patient recruitment continued. Review of all available results, patient follow up and record monitoring continued.

33rd month (March 2017): End of patient recruitment as 227 samples were collected (over target numbers of 219 samples). Original plan of finishing follow up patients but since recruitment process was continued till this time point, follow up for the patients recruited was continued. Data analysis started.

36th month (June 2017): Final data analysis finished.

The preliminary results have been accepted by the Chest Annual Meeting 2017 and will be presented as an abstract in the meeting in October in Toronto, Canada. The details of the project had been written as a manuscript for review of publication in the official journal "Chest" of the American College of Chest Physicians.

Results

Between December 2014 to February 2017, a total of 227 patients undergone bronchoscopy with BAL samples collected and analyzed by GeneXpert. This has exceeded the target of the proposed 219 samples in the research application. Figure 1 shows the flow of patients and samples from study intake to outcome of results from different test modalities. The mean age(SD) of patients was 60.7(15) years. Other demographics and characteristics of the patients are shown in Table 1. Four samples did not yield GeneXpert results because of technical problems in the machine. Among these 4 cases, 1 was positive by BAL TB culture while the other 3 were negative for all tests done. These 4 cases were excluded from analysis, leaving 46 positive cases of TB (those with at least 1 positive result in overall samples) and 181 negative cases.

Excluding the 4 samples with no result, 39(17.4%) were positive and 184(82.6%) were negative for GeneXpert. The performance of GeneXpert was evaluated by comparing with the results of BAL culture, Cobas Taqman TB-PCR and results from overall pooled samples respectively (case was defined as TB if any one of the above tests was positive). The values are summarized in table II. Table III compares the performance of different tests with reference to BAL TB culture and the results with reference to overall pooled samples respectively.

Table IV describes the clinical characteristics of the 9 cases with negative GeneXpert results. There was no rifampicin resistance, neither in GeneXpert nor from drug susceptibilities testing of positive cultures. Sixteen patients had nontuberculous mycobacteria, 10 were recovered from sputum culture while 6 from BAL fluid culture. Their GeneXpert results were all negative. There were 5 patients with autoimmune diseases and were undergoing immunosuppressant therapy. One of them was on infliximab for rheumatoid arthritis. The BAL AFB smear, culture, GeneXpert and Cobas Taqman BAL

TB-PCR were all positive. There were 5 HIV-positive patients who had negative TB-results in all investigations.

Discussion

Merits of different diagnostic tests

Using BAL culture as the standard reference test, BAL AFB-smear has the highest value of 100% in terms of both specificity and positive predictive value, but very low sensitivity with a value of 21% only (Table III). Cobas Taqman TB-PCR test had a sensitivity of 76.3% whereas GeneXpert was 83.8%. Both Cobas Taqman PCR and GeneXpert had comparable specificity and negative predictive values of ~96% (table III). This observation has also been reported in another study.[7] The high specificity and positive predictive value of BAL AFB-smear suggested that this test was useful to rule in active TB while PCR tests were useful to rule out active TB in clinically suspected patients with the relatively higher negative predictive values. In particular, GeneXpert had a more satisfactory "all round" performance considering the sensitivity was the highest among the 3 tests.

Performance of GeneXpert

In clinical practice, a diagnosis of TB would be established when a single test was positive in clinical suspicious cases. When considering the overall samples results (Table III), i.e. pooled results of BAL smear, culture and Cobas Taqman TB-PCR, GeneXpert had high sensitivity, specificity and negative predictive values. The positive predictive value was, however, slightly lower than Cobas Taqman TB-PCR and BAL AFB-smear in our study population. This could be explained by the three cases which were classified as "false positive" as all other diagnostic tests were negative. Two cases showed clinical improvement after anti-TB treatment (details discuss below). Therefore, if the clinical outcomes were also considered, the false positive GeneXpert cases would be actually classified as true positive and would then give a higher positive predictive value.

GeneXpert has a high concordance when compared to the Cobas Taqman TB PCR, both the sensitivity and specificity had a high value of ~96% (Table II). There were 7 GeneXpert positive samples with negative Cobas Taqman PCR results, of which 6 samples showed MTB detection were low and one was medium. They were all BAL AFB-smear negative. These accounted for the higher sensitivity of GeneXpert when compared to the Cobas Taqman TB-PCR with references to other tests (Table III).

The sensitivity of Cobas Taqman TB-PCR or GeneXpert was in general lower than the respective specificity in smear negative respiratory samples (table III). Similar observation was also noticed in GeneXpert as summarized in the Cochrane review.[9] Four of the 7 cases with negative Cobas Taqman

TB-PCR had positive MTB culture recovered from either sputum or BAL fluid. The remaining 3 cases were negative in all other tests except GeneXpert. Two patients were put on empirical anti-TB treatment with good response, both clinically and radiologically, one patient defaulted follow up. It was possible that the mycobacteria load was very low in these GeneXpert "false positive" samples as reflected by the results of the GeneXpert was "MTB detection low" and the Cobas Taqman TB-PCR was also unable to detect. According to the manufacturer's instructions, the detection limit of the Cobas TaqMan MTB assay is 0.33 to 0.83 CFU (95% CI) per PCR. One of the determinants of GeneXpert sensitivity was correlated to the bacteria load in a study comparing samples from different body compartments.[10]

There were 9 false negative results of GeneXpert (Table IV). Most of the cases were also negative with the Cobas Taqman TB-PCR, except case number 2. This case had history of old TB, with typical X-ray features of active TB yet BAL AFB-smear and TB culture were all negative. Cobas Taqman TB-PCR PCR was the only positive test. It was not possible to determine if the positive TB-PCR was related to the old TB or the active TB as no TB bacillus could be isolated. The resolution of X-ray abnormality implied that this was probably a genuine case of active pulmonary TB. The diagnosis of the other 8 cases was either confirmed by TB culture or biopsy results: 7 cases were either BAL or pleural fluid TB culture positive, while one case had biopsy that showed granulomatous lesion. From the clinical perspective, GeneXpert performed similarly as the Cobas Taqman TB-PCR test. Yet culture for MTB still remains crucial for TB diagnosis.

Conclusion

GeneXpert is a fast and simple test for identifying active infection in clinical suspicious cases of pulmonary TB. The performance is similar to a Cobas Taqman TB-PCR on BAL samples, but has the advantage of generating results more quickly. In a TB-intermediate burden area, other complimentary tests should be performed if resources permit, especially TB culture since it supplements cases with negative results in GeneXpert or with Cobas Taqman TB-PCR test.

References

1. Global Tuberculosis Report 2016. WHO Press 2016.
2. Davis JL, Cattamanchi A, Cuevas LE, et al. Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis.* 2013; 13:147-154.
3. Cruciani M, Scarparo C, Malena M, et al. Meta-analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without solid media, for detection of mycobacteria. *Journal of Clinical Microbiology.* 2004; 42:2321-2325.

4. WHO. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update., 2013
5. Jafari C, Ernst M, Kalsdorf B, et al. Comparison of molecular and immunological methods for the rapid diagnosis of smear-negative tuberculosis. *International Journal of Tuberculosis & Lung Disease.* 2013; 17:1459-1465.
6. Chang K, Lu W, Wang J, et al. Rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF assay: A meta-analysis. *Journal of Infection.* 2012; 64:580-588.
7. Teo J, Jureen R, Chiang D, et al. Comparison of two nucleic acid amplification assays, the Xpert MTB/RIF and the Amplified Mycobacterium Tuberculosis Direct (MTD) assay, for the detection of Mycobacterium tuberculosis in respiratory and non-respiratory specimens. *Journal of Clinical Microbiology.* 2011
8. World Health Organization: Tuberculosis country profiles: Hong Kong
9. Steingart KR, Schiller I, Horne DJ, et al. Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database of Systematic Reviews.* 2014:CD009593.
10. Theron G, Peter J, Calligaro G, et al. Determinants of PCR performance (Xpert MTB/RIF), including bacterial load and inhibition, for TB diagnosis using specimens from different body compartments. *Scientific Reports.* 2014; 4:5658.

Figure 1

Flow of patients and samples from study intake to outcome of results from different test modalities

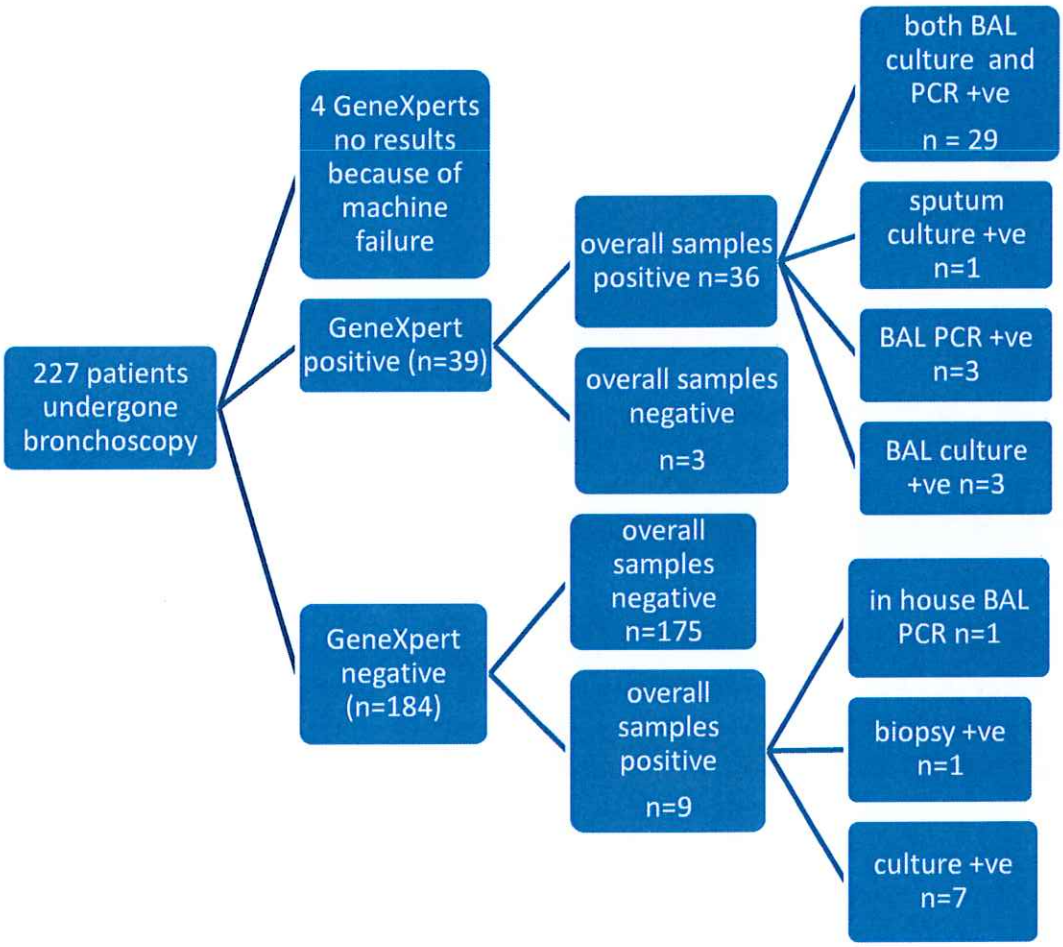

Table 1 Demographic characteristics of 227 patients who undergone bronchoscopy

	N (%)
Gender	
Male	143(63)
Female	84(37)
Presenting Symptoms	
Cough	159(70)
Haemoptysis	85(37.4)
Fever	51(22.5)
Weight loss	41(18.1)
No symptoms	23(10.1)
Medical Comorbidities	
Good past health	50(22)
Cancer	37(16.3)
Cardiovascular illnesses	36(15.8)
Diabetes	22(9.7)
Respiratory illnesses	21(9.3)
immunocompromised	14(6.2)
Old TB	4(1.8)

Table II

Performance of GeneXpert using different diagnostic methods as comparison

GeneXpert / Diagnostic Standard	Sensitivity(95%CI)	Specificity(95%CI)	Positive predictive value(95%CI)	Negative predictive value(95%CI)
BAL culture	83.8(68-93.8)	96.1(92.2-98.4)	81.6(67.9-90.3)	96.7(93.3-98.4)
Cobas Taqman TB PCR	96.9(84.2-99.9)	96.2(92.4-98.5)	82.1(68.8-90.5)	99.4(96.3-99.9)
Overall pooled samples*	80(65.4-90.4)	98.3(95.2-99.7)	92.3(79.5-97.4)	95.1(91.6-97.2)

* Overall pooled samples = BAL smear, BAL culture, Cobas Tagman TB-PCR, GeneXpert and biopsy if available

Table III Performance of BAL smear, In house TB PCR, GeneXpert using BAL culture or overall pooled samples‡ as standard test

	BAL culture			
	Sensitivity %(95%CI)	**Specificity %(95%CI)**	**Positive predictive value %(95%CI)**	**Negative predictive value %(95%CI)**
GeneXpert	83.8(68-93.8)	96.1(92.2-98.4)	81.6(67.9-90.3)	96.7(93.3-98.4)
Cobas Taqman TB PCR	76.3(59.8-88.6)	97.8(94.5-99.4)	87.9(73-95.1)	95.2(91.9-97.3)
BAL smear	21(9.6-37.3)	100(98-100)	100*	86(83.9-87.9)
	Overall pooled samples‡			
GeneXpert	80(65.4-90.4)	98.3(95.2-99.7)	92.3(79.5-97.4)	95.1(91.6-97.2)
Cobas Taqman TB PCR	73.3(58.1-85.4)	100(97.9-100)	100*	93.6(89.9-95.9)
BAL smear	17.8(8-32)	100(97.9-100)	100*	82.8(80.7-84.6)

* No false positive case

‡ Overall pooled samples = BAL smear, BAL culture, Cobas Tagman TB-PCR, GeneXpert and biopsy if available

Table IV

Characteristics of false-negative cases in using GeneXpert for BAL fluid

	Age/ gender	symptoms	comorbidity	History of old TB	CXR/CT abnormalities	Positive tests	Outcome after antiTB treatment
1	51/F	cough	History of right hemicolectomy for dysplasia	no	Military nodules in random locatiions	Transbronchial biopsy showed non-necrotizing granuloma	Resolution of military nodules
2	57/M	haemoptysis	History of myofibroblastic sarcoma of tonsil	yes	Right upper lobe cavitation and consolidation	BAL TB PCR positive	Resolution of XR abnormality
3	45/F	Fever with right side pleurisy	Good past health	no	Right side pleural effusion with consolidation	Pleural fluid grew MTB	Ongoing treatment with favorable response
4	58/M	haemoptysis	diabetes	no	Left upper lobe cavitation	Sputum and BAL MTB culture positive	Resolution of XR abnormality
5	56/M	Asymptomatic, accidental findings of CXR abnormalities	History of stroke	no	Right upper lobe tree-in-bud lesion	BAL MTB culture positive with necrotizing granuloma in biopsy	Resolution of XR abnormality

6	39/F	Fever with right pleural effusion	Good past health	no	Right pleural effusion with consolidation	BAL and pleural fluid culture grew MTB, pleural biopsy AFB smear +ve	Resolution of XR abnormality
7	82/M	Weight loss with hypercalcemia	Diabetes and renal cell carcinoma	yes	Bilateral upper lobes small nodules with small right side pleural effusion	BAL MTB culture positive	Clinical improvement
8	53/M	asymptomatic	Laryngeal and pyriform fossa cancer	no	PET CT accidental findings of lung nodules	BAL MTB culture positive	Improvement of abnormal lesion
9	86/M	asymptomatic	Diabetes, hypertension, ischemic heart disease	no	Centrilobular nodules in upper lobe	Repeat BAL MTB culture positive	Resolution of XR abnormality

Appendices

Research Outputs

The preliminary results have been accepted by the Chest Annual Meeting 2017 and will be presented as an abstract poster in October 2017 in Toronto, Canada.

The details of the project have been written up as a manuscript and has been submitted for publication in the official journal "Chest" of the American College of Chest Physicians. It is currently under review at the time of writing.

The abstract for the Chest Annual Meeting 2017 is attached below:

Clinical application of GeneXpert on bronchoalveolar lavage samples in management of tuberculosis (TB) in intermediate burden area

Limited experience presently exists on clinical use of GeneXpert (Xpert) on bronchoalveolar lavage (BAL) fluid samples obtained from patients clinically suspected of pulmonary TB. We recruited sputum acid-fast-bacilli (AFB) smear negative patients who were offered bronchoscopy. BAL fluid was collected for AFB smear, TB culture and conventional TB PCR. An extra 5 ml BAL fluid was collected for Xpert. Performance of Xpert was compared to each of the other methods of detection. Cases were considered to have TB if any one of the above samples was positive (overall samples).

From December 2014 to December 2016, a total of 211 samples with complete data for analysis were collected. Patients' mean+SD age was 60.4+14.9 years, of which 137 were males and 78 were females. Cough and haemoptysis were the presenting symptoms in 70% and 37.4% respectively. Apical shadows in chest X-ray (CXR) were more common in Xpert positive cases ($X2=10$, $p=0.02$). For CT abnormalities, there were no significant differences in presence/absence of ground glass, tree in buds and consolidation, between Xpert positive or negative cases. However, there were more cavitations and pleural effusions in Xpert positive cases ($X2=10$ and 12, $p=0.02$ and 0.06 respectively). Sensitivities of Xpert ranged from 83 to 100% when compared to each other category of testing, with 79% for overall samples. Similar comparisons showed specificities ranged from 85.3% to 96%, while overall specificity was 98%. The positive predictive values of Xpert compared to each other category of testing ranged from 18.9% to 81.1%, with overall value of 91.9%, while negative predictive values ranged from 96.5% to 100%, with overall value of 94.8%.

From practical point of view in clinical practice, treatment would be started with any positive result. It would therefore be more useful to focus on overall performance rather than individual comparison values. Out of the 9 false negative Xpert samples (8 were conventional TB PCR negative): 6 were diagnosed by BAL culture, 1 by biopsy which showed necrotizing granuloma, 1 by AFB positive pleural biopsy, and another one by conventional TB PCR. These cases helped explain the relatively lower sensitivities in specific situations. On the other hand, comparison of performance with conventional TB PCR showed Xpert's relative higher specificity. There were only 3 false positive cases, in which the MTB detection was low, probably cases with low bacillary load. Of these, 2 were put on empirical treatment with favorable clinical responses, while one defaulted follow up. If the clinical responses were also taken as evaluation, then the positive predictive values would be even higher.

In summary, in an intermediate TB burden area like Hong Kong, Xpert has high specificity and similar performance as conventional PCR. Technical simplicity made it useful tool to rule in TB for initiating early treatment in clinical suspicious cases. However, it cannot replace other investigations as the only test for diagnosing pulmonary TB.