Role of Clinical Judgment in the Application of a Nucleic Acid Amplification Test for the Rapid Diagnosis of Pulmonary Tuberculosis*

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Background: Several nucleic acid amplification (NAA) tests for *Mycobacterium tuberculosis* (MTB) have been licensed for the rapid diagnosis of active pulmonary tuberculosis (PTB) in respiratory secretions. There is uncertainty however regarding the practical application of these tests in clinical decision making.

Objective: To evaluate the utility of the COBAS AMPLICOR assay (Roche Diagnostics; Singapore) for MTB as applied by specialists for the rapid diagnosis of PTB in the routine clinical setting.

Design: A prospective study of consecutive patients suspected of PTB and tested with the AMPLICOR assay under the care of respiratory physicians. The final diagnosis was based on all relevant clinical information after at least 3 months of follow-up. Accuracy of the NAA test was compared with that of the initial expectant treatment. Expectant treatment was based on an integrated approach that incorporated clinical evaluation with results of direct smear and NAA tests.

Results: The incidence of PTB in 168 patients was 32%. The basis for expectant treatment of PTB was positive smear result in 47%, clinical suspicion in 26%, and positive AMPLICOR result in 23%. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the AMPLICOR test were 77%, 100%, 99%, 90%, and 93%, respectively. In comparison, they were 96%, 97%, 94%, 98%, and 97%, respectively, for the integrated clinical approach.

Conclusions: In the rapid diagnosis of PTB, the clinical judgment of specialists augmented the utility of the NAA test: (1) specialists selected patients with high-to-moderate pretest probabilities, (2) they commenced treatment promptly on a positive NAA test result, and (3) they were willing to start treatment in some patients on the basis of high clinical suspicion despite negative smear and negative NAA test results.

Key words: AMPLICOR; *Mycobacterium tuberculosis*; nucleic acid amplification; pulmonary tuberculosis; rapid diagnosis

Abbreviations: CI = confidence interval; MOTT = mycobacteria other than tuberculosis; MTB = *Mycobacterium tuberculosis*; NAA = nucleic acid amplification; PTB = pulmonary tuberculosis; TB = tuberculosis

The definitive diagnosis of active pulmonary tuberculosis (PTB) usually requires the isolation of *Mycobacterium tuberculosis* (MTB) from respiratory secretions. Even with automated liquid culture methods, this process may take up to 6 weeks. Most attending doctors and their patients will prefer not to wait for so long before making a decision on whether to start anti-tuberculosis (TB) treatment. Thus, it is common practice to commence early expectant treatment for PTB based on provisional diagnosis before bacteriologic confirmation. This is a clinical decision based primarily on detecting symptoms that are consistent with a subacute or chronic respiratory infection, recognizing typical features of active PTB on plain chest radiographs, and identifying acid fast bacilli in expectorated sputum.1 This expectant approach to the early diagnosis of PTB, though widely practiced, is not very accurate.2,3 In up to 30% of patients hospitalized with active PTB, the diagnosis may be missed and, thus, appropriate treatment delayed.4,5 Greenaway et al5 showed in a large,

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multicenter, prospective study that delayed treatment of PTB is strongly associated with late intensive care admissions, in-hospital mortality, and nosocomial transmission. Conversely, some patients who do not actually have PTB may be administered anti-TB treatment inappropriately on clinical grounds. These patients will then incur the consequences of both toxicity from anti-TB drugs and delayed diagnosis of other illnesses such as malignancy.

Therefore, the advent of rapid nucleic acid amplification (NAA) tests for MTB is seen as a major breakthrough in the management of PTB.6–9 Several commercial NAA tests have undergone validation and are licensed for routine testing of sputum. They have specificities of close to 100% but variable sensitivities, especially in smear-negative disease, where a rapid diagnostic test is most needed. There is uncertainty even among experts regarding how these tests should be utilized. An American Thoracic Society workshop failed to reach a consensus on the appropriate use of these tests in smear-negative patients; however, the American Centers for Disease Control and Prevention recommends that NAA test be performed on the very first sputum specimens collected.9 By contrast, Schluger10 suggests that NAA tests should not be performed on samples from patients with low clinical suspicion of PTB. Barnes11 concurs with him and would furthermore decline to use these tests in patients with a very high likelihood of PTB. Despite such uncertainties, these tests have entered the realm of everyday practice in many institutions where there is rising demand for rapid tests for PTB.12

In a prospective study13 of smear-negative PTB, we concluded that the utility of NAA tests may be limited by overestimation of pretest probability of active disease. In a subsequent study14 of on-demand requests for NAA testing by house staff, we found that the rapid test was more accurate than clinical judgment of inexperienced doctors and that the optimal approach was to limit testing to patients with high or intermediate risk of PTB. Thus, the aim of the present study was to evaluate the utility of a commercial NAA test for the rapid diagnosis of PTB in routine clinical practice by respiratory specialists.

Materials and Methods

Patients and Clinical Setting

Between May 2000 and April 2001, we enrolled consecutive adult patients (> 14 years of age) suspected of having active PTB. Singapore is an intermediate prevalence country for PTB with 45 new cases reported per 100,000 population annually. The COBAS AMPLICOR (Roche Diagnostics; Singapore) test for MTB had been available on demand at the microbiology depart-

ment of the hospital since mid-1998.12 Enrolling physicians were pulmonary specialists experienced in the evaluation of patients for active PTB in a university hospital. The consensus among the investigators in our institution was that it should be utilized only as a confirmatory test in patients with high-to-intermediate risk of active PTB.10,11,13,14 The estimation of pretest probability of active PTB has been described previously and is based on a review of the presenting history, clinical charts, initial laboratory data, which included results of AFB smear, and chest radiographs.13,14 These were loose guidelines and not firm practice protocols, and the attending specialists were encouraged to exercise judgment on appropriate tests and treatment. Patients were recruited only if they were managed by pulmonary specialists who requested that their respiratory secretions be tested for MTB by the AMPLICOR assay. Thus, in practice, only patients deemed to have high-to-intermediate pretest probability of active PTB and had AMPLICOR test ordered by a pulmonary specialist on clinical grounds were enrolled.

Respiratory secretions included spontaneously expectorated sputum and tracheal aspirates from intubated patients. Additional investigations such as induced sputum and bronchoscopy were performed at the discretion of the attending physician; however, it was not the usual practice in the hospital, during the period of this study, to utilize either induced sputum or bronchoscopy in the diagnosis of PTB. Patients with only pleural or extrapulmonary disease and those already receiving anti-TB medication were excluded.

Microbiological Tests

Conventional Mycobacterial Tests: Respiratory specimens were decontaminated and digested by mixing 0.5% N-acetyl-L-cysteine-2% NaOH with an equal volume of the specimen. After incubation at 36°C for 25 min, phosphate buffer (pH 6.8) was added to the 25-mL mark and the contents of the tube gently mixed prior to centrifugation at 3,500g for 15 min. The supernatant was then discarded and the sediment resuspended in 0.5-mL phosphate buffer. One hundred microliters of the decontaminated specimen were placed in a 2-mL safe-lock tube ready for processing. Direct smears were prepared for screening by fluo-

rochrome staining (auramine O) and confirmation by Ziehl Neelsen staining. The remainder of the specimen was inoculated into radiometric broth medium for culture and sensitivity testing (BACTEC; Becton Dickinson Diagnostics Instruments System; Sparks, MD).

Direct Amplification Assay (AMPLICOR Test): This was pre-

formed according to the instructions of the manufacturer. Fifty microtubes of working master mix were introduced into each amplification tube (one tube for each specimen, plus a positive and a negative control tube). The master mix contains an “internal control” that allows for identification of any specimens containing inhibitors that could hinder target DNA amplification and, thus, potentially produce false-negative results. Fifty microtubes of each specimen and each control were placed into its appropriate amplification tube, which was then tightly closed. The specimens were then placed into the COBAS AMPLICOR analyzer for automated amplification and MTB detection. Specimens that gave negative MTB and internal control results were purified using the QUamp DNA kits (Qugen; Hilden, Germany).

Definitions and Diagnoses

An Integrated Approach to Early Diagnosis and Treatment of PTB: Early treatment is defined as expectant treatment of PTB before isolation of MTB from culture. This was based on integrating clinical judgment with results of initial clinical evalu-

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ation and rapid microbiologic tests such as acid fast bacilli smear, and included results of radiologic investigations, tissue biopsies, and the AMPLICOR test. The attending physicians indicated the basis for making the diagnosis of PTB when they initiated anti-TB treatment. For the Bayesian analysis, the initiation of anti-TB therapy before a final diagnosis if PTB was categorized as a “positive” result with regards to the integrated clinical-AMPLI-
COR approach. No serologic or other immunologic tests were employed. Tuberculin skin testing is not a useful diagnostic test for hospitalized patients in Singapore, and was thus not used as a diagnostic criteria in this study.15

**Final Diagnosis of PTB:** The final diagnosis of active PTB was determined by consensus between at least two respiratory specialists after at least 3 months of patient follow-up. This was primarily based on positive culture results for MTB isolated from respiratory secretions and chest radiologic features consistent with active disease. Patients with culture- and smear-negative PTB were identified from global assessment of all relevant clinical information including CT scanning of the thorax and response to anti-TB treatment. Ambiguities were either resolved by independent review with another chest physician or radiologist or excluded from the analysis.

**Statistical Analysis**

The clinical information and laboratory data were expressed and analyzed on a per-patient basis. Data were collated and the cross tabulations were performed using SPSS 9.0.1 for Windows (SPSS; Chicago, IL). Continuous variables were expressed as means ± SD. Sensitivity, specificity, positive predictive value, and negative predicted value were calculated separately for the AMPLICOR test and the integrated approach to the rapid diagnosis of PTB. Ninety-five percent confidence intervals (CIs) were estimated according to the binomial distribution. Bayes’ theorem was used to calculate the probability of active PTB conditioned by results of either the AMPLICOR test or the integrated approach to the early diagnosis of PTB as a function of the pretest probability of PTB.16 The software was acquired from the Centre for Evidence Based Medicine, Mount Sinai Hospital–University Health Network, Department of Medicine, University of Toronto, ON, Canada (http://www.cebm.utoronto.ca/practise/ ca/statscal/). For the Bayesian analysis, the initiation of anti-TB therapy before a final diagnosis if PTB was categorized as a “positive” result with regards to the integrated clinical-plus AMPLICOR approach.

**Results**

During the study period, 179 consecutive patients were enrolled. Eleven patients were excluded for the following reasons: 1 patient was already receiving anti-TB treatment, 4 patients did not have at least one valid specimen, and the final diagnosis was not established with confidence in 6 patients due to incomplete or inconsistent clinical information. Results of the remaining 168 patients were available for analysis.

There were 112 men and 56 women (mean age ± SD, 56 ± 18 years; range, 18 to 88 years). The predisposing factors to active PTB were diabetes mellitus in 32 patients (19%), immunosuppression from corticosteroid treatment in 6 patients, hemoncologic diseases in 8 patients, alcoholism in 3 patients, and HIV infection in 2 patients. The majority of specimens were expectorated sputum, with < 5% from induced cough or bronchoscopic lavage.

As shown in Table 1, active PTB was diagnosed in 53 of 168 patients (32%) while 10 patients (6%) had nontuberculous mycobacteria infection. Among the 53 patients with active PTB, 25 patients were smear positive, 41 patients returned positive AMPLICOR test results, and 43 had positive culture findings for MTB (Table 2). Among the 10 patients with nontuberculous mycobacteria infection, 3 patients were smear positive but none returned positive AMPLICOR test results. Community-acquired pneumonia and bronchogenic carcinoma were the main diagnoses in patients who did not have PTB (Table 1).

When mycobacterial culture was used as a standard, the AMPLICOR test had a sensitivity of 88% (95% CI, 76 to 95%) and specificity of 97% (95% CI, 93 to 99%). However, when clinically defined cases were added to patients with a final diagnosis of active PTB, the AMPLICOR test had a lower sensitivity of

| Table 1—Final Diagnoses of Patients |
|-------------------------------------|-----------------|
| Diagnoses                           | No. (%)         |
| Active PTB                          | 53 (32)         |
| Culture-positive PTB                | 43              |
| Culture-negative PTB                | 10              |
| Nontuberculous mycobacteria         | 10 (6)          |
| Other respiratory diseases          | 103 (61)        |
| Respiratory infections (including two cases each of pleural empyema, HIV, aspergillosis) | 33 |
| Malignancy (including three patients with lymphoma, and one patient each with alveolar cell carcinoma and mesothelioma) | 23 |
| Stable radiologic scars (including inactive PTB [n = 14], silicosis [n = 2], and radiation injury [n = 2]) | 21 |
| Diffuse interstitial pneumonitis (six patients each with cryptogenic pneumonias and collagen diseases) | 12 |
| Airway diseases (COPD [n = 6], bronchiectasis [n = 5], and chronic bronchitis [n = 2]) | 13 |
| Pulmonary embolism                   | 1               |
| Nonrespiratory sepsis               | 2               |
| Total                               | 168 (100)       |

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77% (95% CI, 64 to 86%) but maintained a high specificity of 100% (95% CI, 96 to 100%).

As shown in Table 3, treatment for PTB was initiated in 54 patients by their attending doctors on an expectant basis (the integrated clinical approach). This occurred before knowing the results of mycobacterial cultures and the final diagnosis of active PTB. The initial treatment was based on a positive smear result in 25 patients, positive AMPLICOR result in 12 patients, consistent radiologic features in 10 patients, and consistent histology in 7 patients. Anti-TB treatment was started before the AMPLICOR test was reported to be positive in three patients. Anti-TB treatment was inappropriate and the initial diagnosis incorrect in three patients who were deemed, in the final analysis, not to have active PTB. None of the patients who were infected with mycobacteria other than tuberculosis (MOTT) received treatment for PTB.

Another two patients had active PTB confirmed by positive mycobacterial culture results, as shown in Table 3; however, the diagnosis was missed initially and they did not receive early anti-TB treatment. One patient had a negative smear and AMPLICOR test results and was recalled for treatment following return of positive culture finding. Another patient returned a positive AMPLICOR test result on the day he died and thus did not receive appropriate treatment at all.

The diagnostic accuracy and clinical utility of the AMPLICOR test alone and that of the integrated approach that incorporated the AMPLICOR test with clinical judgment are charted in Figures 1, 2, respectively. At the prevalence of active PTB (pretest probability) in this study of 32%, the AMPLICOR test showed higher specificity (100% vs 97%) and higher positive predictive values (99% vs 94%) but lower sensitivity (77% vs 96%) and lower negative predictive values (90% vs 98%) than the integrated clinical approach. The overall accuracy of the

Table 2—Results of Microbiological Tests in Relation to Final Diagnosis of Active PTB*

<table>
<thead>
<tr>
<th>Microbiological Test Results</th>
<th>Active PTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziehl Neelson Staining</td>
<td>AMPLICOR Culture</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
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<tr>
<td>Negative</td>
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<tr>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Total</td>
<td>115</td>
</tr>
</tbody>
</table>

*Data are presented as No.

Table 3—Results of Rapid Microbiologic Tests in Relation to Rationale for Initial Diagnosis of Active PTB*

<table>
<thead>
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<th>Microbiological Test Results</th>
<th>Basis for Initial Diagnosis of Active PTB</th>
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</thead>
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<tr>
<td>Ziehl Neelson Staining</td>
<td>AMPLICOR Decision AMPLICOR Culture Results</td>
</tr>
<tr>
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<td>Negative</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
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<td>Positive</td>
<td>Negative</td>
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†Empiric treatment was wrongly initiated for 3 patients in this group; therefore, only 11 of 14 patients in this group had active PTB.
‡Anti-TB treatment started on the basis of clinical suspicion before knowing AMPLICOR test results.
§This patient was not treated for PTB; he returned a positive AMPLICOR assay result on the day he died.

*Data are presented as No.

Figure 1. This figure plots the relation between the probability of PTB before undertaking the AMPLICOR test (pretest probability, horizontal axis) and after the AMPLICOR test results are known (posttest probability, vertical axis) in patients who return positive (+ve) AMPLICOR test results (bold line) vs patients who return negative (–ve) AMPLICOR test results (thin line).
integrated clinical approach was slightly higher than the AMPLICOR test. This superior performance of the integrated clinical judgment was observed for the whole group of patients, where the overall accuracies were 97% vs 93%, respectively, and also for the 140 patients who were smear negative, where the overall accuracies were 96% vs 90%, respectively. Furthermore, the Bayesian analysis predicts that, as the risk of PTB and pretest probability increase, this dominance of the integrated clinical approach over the AMPLICOR test will also increase.

**Discussion**

The accuracy of commercial NAA tests have been established and validated in a large number of clinical trials. More recent studies have estimated the potential clinical utility of these tests in relation to different levels of clinical suspicion and pretest probability. In this study, we have taken a step further and provided information regarding the practical utility of a NAA test in routine clinical practice. We found that, in the use of the AMPLICOR test for the rapid diagnosis of PTB, when specialists interpreted test results and supervised patient management in conjunction with other clinical information, the overall diagnostic accuracy was > 93%. This approach was more accurate than employing the test in isolation. Furthermore, this study has delineated the role of experienced clinicians in patient selection, interpretation of test results, and therapeutic decision making in a real-world setting.

We evaluated the utility of the AMPLICOR test in hospitalized patients under the care of respiratory physicians. We had concluded, from a previous prospective study of patients investigated for smear-negative PTB, that there was a tendency to over investigate for PTB and that this had limited the utility of the rapid test that has high specificity but only moderate-to-low sensitivity in these patients. Following an evaluation of the utility of the AMPLICOR test when ordered by house staff, we had concurred with Schluger and Barnes that these tests should be not be employed in patients with a low clinical suspicion of PTB. We and other investigators believe that the AMPLICOR test should be used to confirm the diagnosis of PTB in patients with an intermediate-to-high likelihood of disease. They should not be used as screen tests to rule out active PTB; therefore, our intention in this study was to limit NAA testing only to patients who were considered by respiratory specialists to have high-to-intermediate risk of PTB. Consequently, we noted a progressive increase in the incidence of PTB from between 5.7% and 15.6% in our two previous studies to 32% in the present study. The sensitivity of the AMPLICOR test varied little from between 44% and 58.3% to 56.9% respectively, while the specificity was consistently close to 100% in all three studies. The results of this study suggests, furthermore, that selection of appropriate patients for further testing and exclusion of low-risk patients from microbiologic testing by experienced clinicians may help to optimize the cost-effectiveness of these new and relatively expensive tests.

In this study, the attending specialists were able, in all instances, to indicate the main reason for making a diagnosis of PTB and for starting anti-TB treatment early. The most common clinical setting for starting anti-TB treatment is detection of a positive smear result in a patient with high clinical suspicion of PTB. This was the case in 25 of 53 patients (47%)
with PTB in this study. The AMPLICOR test result was also positive in all 25 patients, but this information did not contribute directly to the decision to start treatment for TB. By contrast, the three patients who had MOTT and were smear positive but AMPLICOR test negative did not receive anti-TB treatment. Thus, our results indicate that it might not be cost-effective to perform NAA testing in smear-positive patients with frank cavitary disease who have already been started on anti-TB treatment by their attending physicians. This finding is consistent with the suggestion by Barnes
 to avoid testing patients with very high clinical suspicion.

In another 12 patients (23%), treatment for TB was commenced on the basis of a positive AMPLICOR test result despite negative smear findings. This is the result of appropriate interpretation of the results of a confirmatory diagnostic test with high specificity and positive predictive values. In only two patients (4%) was the diagnosis of PTB missed initially. By inference, presumably, 23% plus 4%, a total of 27% of cases, would have been missed if we had not employed the AMPLICOR test. This is very similar to the figure of 30% missed diagnosis and delayed treatment of PTB in studies reported by ourselves and other investigators in studies in which NAA tests were not employed.4,5 Thus, experienced clinicians only requested for the AMPLICOR test in patients with a high likelihood of active disease and, moreover, commenced treatment promptly on a positive result. The cost-effectiveness of this approach that omits investigations for mycobacterial disease in low-risk patients, and also avoids delays and invasive testing in patients with more advanced disease and positive AMPLICOR test results needs further evaluation.

An even more important role for experienced clinicians was in the management of smear- and AMPLICOR-negative patients. Between 20% and 50% of patients with PTB are smear negative. In smear-negative patients, the AMPLICOR test has relatively low sensitivities (57%) and negative predictive values (90%). Thus, if treatment was based solely on test results, we risk not treating approximately one half of the patients with smear-negative PTB. We believe that clinicians should exercise due clinical judgment in patients with negative AMPLICOR test results, and be prepared, in the appropriate setting, to start empiric anti-TB treatment.14 In this study, anti-TB treatment was commenced, despite negative smear and AMPLICOR test results, in 26% of patients with PTB. This gives us some idea with regards to the risk of not treating patients with negative NAA test results and, conversely, the added value of appropriate clinical judgment. For the cohort of patients with an even higher suspicion of PTB and thus higher pretest probably for smear-negative disease as a whole, this risk will increase proportionately if the anti-TB treatment is withheld in all patients who returned negative AMPLICOR assay results (Fig 1).

Clinical judgment, even after consideration of the NAA test results, was associated with lower specificity and lower positive predictive values than the AMPLICOR test alone. This deficiency resulted in overdiagnosis and inappropriate treatment in 6% of patients who received early anti-TB therapy; however, the overall accuracy of the integrated clinical approach was superior because of its much higher sensitivity and negative predictive values. This was the case for the whole group of patients and, even more importantly, for patients who returned negative smear test results. Furthermore, the advantage of this approach over the NAA tests will increase in parallel with the pretest probability of PTB.

This study was intended to be descriptive rather than prescriptive. The limitations include its lack of stringent criteria for patient selection, lack of specific guidelines for starting early empiric anti-TB treatment, and the partially blinded, observational design. There are no validated criteria or consensus agreement on the type of patients who should be investigated for PTB. We studied patients who were selected by and under the care of respiratory specialists, a similar clinical setting in which previous trials of NAA tests have been conducted.21,22 Moreover the NAA test was only performed in patients who, in the opinion of the enrolling physicians, had high-to-intermediate risk of PTB and required further investigations on clinical grounds. The results of this study should therefore be interpreted with caution, and our conclusions should not be extrapolated to provide a basis for standard clinical management for all patients suspected of PTB. In a few patients, the investigators who defined the final diagnosis of PTB also participated, to some degree, in their management and thus were not fully blinded to the initial management decisions; however, the initial decision-making process was documented prospectively at the point of starting anti-TB treatment, and the diagnosis of PTB was based on straightforward clinical, radiologic, histologic, and microbiologic information. We excluded the six patients for whom there was incomplete follow-up or lack of agreement with an independent reviewer.

The strengths of the study include prospective inclusion of all patients in a representative clinical setting and elucidation of decision steps. The performance of the AMPLICOR test is consistent with that observed in previous trials.7,13,14,21 Also, we documented real-world outcomes associated with the direct application of the NAA test in 94% of patients.
enrolled. This enabled us to analyze the various diagnostic options with Bayesian methods and assess their utility more realistically.

We conclude that, for the rapid diagnosis of PTB, the clinical judgment of specialists enhanced the utility of the AMPLICOR test: (1) specialists selected patients with high-to-moderate pretest probabilities of PTB for testing in order to confirm the diagnosis, (2) they commenced treatment promptly on a positive test result, and (3) were willing to start treatment in some patients with high clinical suspicion of PTB despite negative smear and negative AMPLICOR test results. Furthermore, we suggest that the cost-effectiveness of NAA tests may be maximized by excluding patients who are unlikely to have PTB and also those with very high clinical suspicion of active disease from further testing.10,11,13,23 However, formal, prospective trials are needed to evaluate the cost-effectiveness of alternative diagnostic strategies that incorporate NAA tests in relevant clinical settings and in relation to well-defined pretest risk profiles.

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