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Evaluation of the Abbott LCx *Mycobacterium tuberculosis* Assay for Direct Detection of *Mycobacterium tuberculosis* Complex in Human Samples

MARIA GRAZIA GARRINO,[1]* YOURI GLUPCZYNSKI,[1] JOSIANE DEGRAUX,[2] HENRI NIZET,[1] AND MICHEL DELMÉE[2]

Microbiology Laboratory, University Hospital Mont-Godinne, Catholic University of Louvain, Yvoir,[1] and Microbiology Unit, Catholic University of Louvain, Brussels,[2] Belgium

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Seven hundred thirty-seven clinical samples from 460 patients were processed for direct detection of *Mycobacterium tuberculosis* complex by a semiautomated ligase chain reaction commercial assay, the LCx *Mycobacterium tuberculosis* Assay (LCx assay) from Abbott Laboratories. Results were compared to those of direct microscopy and standard microbiological culture. Of 26 patients (5.7%) with a culture positive for *M. tuberculosis*, 22 (84.6%) were found positive by the LCx assay. The sensitivity of the LCx assay was 98% for smear-positive samples and 27% for smear-negative samples. With an overall culture positivity rate for *M. tuberculosis* of 8.3% (61 of 737 samples) and after resolution of discrepant results according to clinical data, the sensitivity, specificity, and positive and negative predictive values of the LCx assay were 78, 100, 95, and 98%, respectively, compared to 85, 100, 100, and 98%, respectively, for culture and 67, 99, 87, and 97%, respectively, for acid-fast staining. In conclusion, the LCx assay proved satisfactory and appears to be an easy-to-use 1-day test which must be used with standard culture methods but can considerably reduce diagnosis time versus culture. However, its clinical interest appears to be limited in our population with low mycobacterial prevalence because of its cost considering the small gain in sensitivity versus direct microscopy.

Rapid diagnosis of *Mycobacterium tuberculosis* infection remains a challenge for every medical laboratory. According to the current Centers for Disease Control and Prevention recommendations, identification and antimicrobial susceptibility testing should be available to clinicians within 2 weeks (25). Direct microscopic examination is straightforward but has poor sensitivity and does not allow differentiation between tuberculous and nontuberculous mycobacteria (NTM). Culture is sensitive and specific but very slow. In such a setting, direct amplification tests (DAT) have been actively developed and evaluated for the rapid diagnosis of mycobacterial diseases, and two commercial assays, the Gen-Probe *Mycobacterium tuberculosis* Direct Test (Gen-Probe, San Diego, Calif.) (1, 6, 15, 17, 21, 27) and the Amplicor *M. tuberculosis* test (Roche Diagnostic Systems, Basel, Switzerland) (4, 5, 8, 10, 18, 23, 28), have already been approved by the Food and Drug Administration for smear-positive specimens, after extensive evaluations of their comparable performance characteristics.

Another amplification assay has been recently introduced, the LCx *Mycobacterium tuberculosis* Assay (LCx assay) (Abbott Laboratories, Chicago, Ill.), which is based on the ligase chain reaction. This amplification assay uses a semiautomated system which allows direct detection of *M. tuberculosis* in clinical specimens (3, 13, 16, 19, 26).

The aim of this study was to assess prospectively the performance of the LCx assay and compare its results with those of microscopic examination and culture for a large number of clinical specimens submitted to the laboratory for the diagnosis of mycobacterial infections.

* Corresponding author. Mailing address: Microbiology Laboratory, University Hospital Mont-Godinne, Ave. Therasse 1, B5530 Yvoir, Belgium. Phone: 32 81 423212. Fax: 32 81 423204. E-mail: garrino@mblg.ucl.ac.be.

Materials and methods. From February to August 1997, we prospectively investigated routine clinical specimens submitted for diagnosis of mycobacterial disease from two university hospitals. Specimens from patients under antituberculous treatment were not included.

All specimens were processed by the *N*-acetyl-L-cysteine–NaOH digestion-decontamination procedure (9). In all cases, half of the resuspended sediment was stored at −20°C for the LCx assay, while the rest was used for acid-fast staining and inoculation onto solid and liquid culture media. Smears were stained with auramine-rhodamine fluorochrome as a screening method, and positive smears were confirmed by Ziehl-Neelsen staining. Two solid slants were inoculated per sample: Lowenstein-Jensen and Coletsos (bioMérieux, Marcy l'Etoile, France). For the liquid medium, BACTEC 12B medium (Becton Dickinson, Aalst, Belgium) was used in one hospital, while the oxygen-sensitive fluorescent medium Mycobacterium Growth Indicator Tube (Becton Dickinson) was employed at the other hospital. Liquid and solid media were incubated at 37°C for 6 and 8 weeks, respectively, and were read twice a week. A culture was considered positive if at least one of the media grew mycobacteria. In addition to conventional biochemical tests, thin-layer chromatography and gas-liquid chromatography were used for isolate identification (20). The LCx assay was performed in accordance with the manufacturer's recommendations on a weekly basis (3).

When discrepancies were observed between the results of direct staining, culture, and the LCx assay, the same decontaminated portion of the specimen was retested by the LCx assay. If the discrepancy persisted, clinical data and results obtained with additional samples from the patient were analyzed. A specimen was considered truly positive for *M. tuberculosis* when a culture positive for *M. tuberculosis* was obtained or if a culture negative for *M. tuberculosis* and a positive LCx assay result were obtained if other concomitant material from

TABLE 1. Comparison of LCx assay results with culture results

Specimens (no.)	No. *M. tuberculosis* positive by culture[a]		No. *M. tuberculosis* negative by culture[b]		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	LCx positive	LCx negative	LCx positive	LCx negative				
All (737)	49	12	10	666	80.3	98.5	83.1	98.2
Smear positive (55)	45	1	2	7	97.8	77.8	95.7	87.5
Smear negative (682)	4	11	8	659	26.7	98.8	33.3	98.4
Respiratory (682)	48	9	4	621	84.2	99.4	92.3	98.6
Nonrespiratory (55)	1	3	6	45	25.0	88.2	14.3	93.8

[a] Total $n = 61$.
[b] Total $n = 676$.

the patient was culture positive or if the patient's clinical history, including chest roentgenograms and actual clinical presentation, was sufficiently indicative of tuberculosis for empirical antituberculosis therapy. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the LCx assay were calculated and compared with culture results and with culture results plus the patient's clinical data.

Results. A total of 737 samples were collected from 460 patients suspected of mycobacterial disease and processed by staining methods, standard cultures, and the LCx assay to evaluate the assay's ability to detect *M. tuberculosis* complex organisms. Six hundred eighty-two were respiratory specimens from 425 patients, including 280 sputum, 312 bronchial aspirate, 68 bronchoalveolar lavage, 4 endotracheal aspiration, and 18 gastric juice aspirate samples. The remaining 55 were nonrespiratory specimens from 35 patients, including 7 cerebrospinal fluid, 8 urine, and 40 exudate samples.

Seventy-one (9.6%) specimens of 737 from 32 (7%) of 460 patients were positive for mycobacteria by culture. Isolates were distributed as follows: 61 (8.3%) *M. tuberculosis* isolates from 26 patients (5.7%) and 10 NTM isolates from 6 patients (1.3%), which included 7 *M. avium* complex isolates, 2 *M. simiae* isolates, and 1 *M. gordonae* isolate.

Fifty-five samples were positive by fluorochrome staining, and all of these were confirmed by acid-fast staining. Forty-six (75.4%) of 61 samples whose culture yielded *M. tuberculosis* were positive for acid-fast bacilli, as were 7 (70%) of 10 samples which were positive by culture for NTM. The two remaining smear-positive samples were culture negative.

Among 59 samples found to be positive by the LCx assay, 49 from 22 patients were concomitantly positive for *M. tuberculosis* by culture. The details of the comparison of LCx assay results with culture results are shown in Table 1. A higher sensitivity was observed for smear-positive samples (97.8% versus 26.7% for smear-negative samples) and for respiratory specimens (84.2% versus 25% for nonrespiratory specimens). None of the 10 samples growing NTM were positive by the LCx assay.

Twenty-two samples gave rise to discrepant LCx assay and culture results. Ten samples were LCx assay positive and culture negative. Seven were from a single patient who had been treated for active tuberculosis 2 years earlier with current clinical suspicion of a relapse; these samples were resolved as truly positive. Two samples were from a patient with other negative specimens and with no signs of tuberculosis, and the last sample, also from a patient with other negative specimens, was confirmed as negative when reassayed. The latter three results were considered false-positive results of the LCx assay.

On the other hand, 12 specimens originating from nine patients were positive for *M. tuberculosis* by culture and yielded negative results with the LCx assay. All of these were considered false-negative results of the LCx assay.

Thirty-eight samples came from 15 human immunodeficiency virus-seropositive patients. Seven patients had positive cultures with positive direct microscopy and were correctly diagnosed by the LCx assay (five patients with tuberculosis and two with other mycobacterial disease).

Table 2 summarizes the comparison of LCx assay results with the resolved results (culture plus clinical data). For an overall sensitivity of 78%, there was still a significant difference in sensitivity between smear-positive and smear-negative specimens (98 versus 38%), while the difference between respiratory and nonrespiratory specimens was reduced (79 versus 70%).

The results of the LCx assay, culture, and microscopic examination were then compared with the clinical resolved results for the 737 specimens (Table 3) from the 460 patients. Seventy-two specimens from 27 patients gave results consistent with a clinical diagnosis of tuberculosis. Sixty-one (85%) of 72 were positive for *M. tuberculosis* by culture, 56 (78%) of 72 were positive by LCx assay, and 48 (67%) of 72 were positive for acid-fast bacilli. Twenty-three (85%) patients of 27 with a

TABLE 2. Comparison of LCx assay results with culture results plus clinical data (resolved results)

Specimens (no.)	No. resolved as *M. tuberculosis* positive[a]		No. resolved as *M. tuberculosis* negative[b]		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	LCx positive	LCx negative	LCx positive	LCx negative				
All (737)	56	16	3	662	77.8	99.5	94.9	97.6
Smear positive (55)	47	1	0	7	97.9	100.0	100.0	87.5
Smear negative (682)	9	15	3	655	37.5	99.5	75.0	97.8
Respiratory (682)	49	13	3	617	79.0	99.5	94.2	97.9
Nonrespiratory (55)	7	3	0	45	70.0	100.0	100.0	93.8

[a] $n = 72$.
[b] $n = 665$.

TABLE 3. Comparison of LCx assay, culture, and microscopy results with clinical diagnosis of tuberculosis

Method and result (no. of samples)	No. of specimens[a]		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	TB^+	TB^-				
LCx assay						
Positive (59)	56	3[b]	78	100	95	98
Negative (678)	16	662[c]				
Culture						
Positive (61)	61	0	85	100	100	98
Negative (676)	11	665[c]				
Microscopy						
Positive (55)	48	7[d]	67	99	87	97
Negative (682)	24	658				

[a] TB^+, tuberculosis positive (total $n = 72$); TB^-, tuberculosis negative (total $n = 665$).
[b] One sample was negative when reassayed.
[c] Including 10 samples positive for NTM.
[d] Seven specimens were culture positive for NTM and LCx assay negative.

diagnosis of tuberculosis were correctly diagnosed by the LCx assay, and 2 of them had smear-negative samples.

Discussion. The LCx assay is a commercial, direct nucleic acid amplification test, and it is among the first semiautomated tests, along with the Roche Cobas Amplicor *Mycobacterium tuberculosis* assay (11, 22, 30). Although DNA extraction is still a long manual phase absorbing the major portion of the manpower involved, the automation of the amplification, hybridization, and detection steps offers significant advantages with a hands-off time of about 2.5 h after specimen preparation. A run of samples (20 clinical specimens and four controls) is completed in about 5 to 6 h.

Most of the studies evaluating different DAT include an excess of positive specimens, which artificially increases prevalence by comparison with the real epidemiologic situation (14). Thus, sensitivity results according to culture and clinical diagnosis, which are reported in the recent literature, vary within a range of 80 to 92% for home-made PCR (1, 7, 12, 17, 24), 67 to 87% for the Amplicor test (8, 18, 28), 82 to 98% for the GenProbe direct test (1, 15, 17, 21, 27, 28), and 78 to 96% for the LCx assay (3, 13, 16, 26). For all of these methods, specificity is always excellent, within 96 to 100%. However, when the prevalence of positive specimens is closer to the real situation, the sensitivity decreases to 86, 70, 71, and 77%, respectively, for home-made PCR, the Amplicor test, the Genprobe direct test, and the LCx assay (6, 7, 19, 23). We therefore decided not to include samples from patients undergoing active antituberculosis treatment (14). With a prevalence of 8.3% of samples culture positive for 5.9% of patients with a clinical diagnosis of tuberculosis, the performance of the LCx assay in our evaluation (sensitivity of 78% and specificity of 99%) is very much in line with that in former studies (19). When analyzing the discrepant results after resolution according to clinical data, three results were considered false positives. Contamination could be a reasonable explanation for one sample, because when the same DNA extract was reassayed, the sample was negative. The other two specimens were from a patient with no clinical signs of tuberculosis. Sixteen specimens yielded false-negative results with the LCx assay. This could possibly be due to a low number of microorganisms and/or to their nonuniform distribution in the clinical samples. Indeed, six specimens were from patients with previous LCx-positive samples, which supports the assertion that, as with smear and culture analyses, more than one sample from each patient should be tested to allow sufficient accuracy of detection of *M. tuberculosis* in specimens by the LCx assay. The 10 remaining samples were from four patients for whom only culture results allowed a diagnosis of tuberculosis (smear negative and LCx assay negative). Hence, these results explain the low sensitivity results (38%) we obtained in our evaluation of smear-negative specimens. On the other hand, for two patients with smear-negative specimens, an early diagnosis of tuberculosis could be made thanks to the positive LCx assay results. However, in the first case, we received additional samples 2 days later with smear-positive results so that, only 1 patient with smear-negative samples of the 460 patients tested really benefitted from this DAT in terms of rapidity of diagnosis and treatment instauration. The real advantage of this test appeared for smear-positive specimens because NTM and *M. tuberculosis* are both readily detected by fluorescence microscopy (29) and are almost impossible to distinguish by smear alone. A diagnosis of both tuberculosis and infection with NTM should initially be considered until a more definite diagnosis can be made, especially in selected populations, such as the AIDS patient population. We received samples from 15 human immunodeficiency virus-infected patients, 7 of whom had smear-positive samples. Only two patients were infected with NTM and were correctly diagnosed by the LCx assay. In our study, the PPV of the LCx assay for smear-positive samples were found to be significantly higher than that for smear-negative samples (96 versus 33%) (Table 1), as for the other approved DAT (2). Conversely, the PPVs of smear and LCx assay results were similar (87 and 95%, respectively) (Table 3) because, unfortunately, the proportion of specimens smear positive for NTM was low in the period chosen for the study. To really benefit from the rapidity afforded by a same-day automated method, testing should be performed every day. Although theoretically possible, this is not practical in most laboratories due to the cost. Hence, due to the four controls and calibrators for a run of a maximum of 20 specimens, the cost per test, including reagents and manpower, varies from about $30 if 20 specimens are processed together to $200 if a single specimen must be run alone. To perform this test on a daily basis would only be possible in reference or central laboratories. In our setting, it would be done only once a week, thus undermining a great part of the argument for rapidity.

We conclude that the LCx assay demonstrates very satisfactory performance in terms of sensitivity and specificity for smear-positive specimens, allowing rapid confirmation of positive smear results as true tuberculosis. Such features may be of considerable importance for laboratories dealing with a high proportion of infections caused by NTM, such as in the AIDS patient population. It offers the advantage of semiautomation, which saves labor and allows a same-day result. On the other hand, the assay's performance obtained with specimens negative by direct examination is not sufficient to warrant its use on a routine basis, and this test cannot replace standard culture and susceptibility testing for mycobacteria. Moreover, the cost linked to calibrators and controls is such that this technology is probably suitable only for reference laboratories processing large series of specimens and having good communication with clinicians because of the possibility of both false-positive and false-negative results.

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