Case Studies in Cost Effectiveness of Molecular Diagnostics for Infectious Diseases: Pulmonary Tuberculosis, Enteroviral Meningitis, and BK Virus Nephropathy

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Pathogen genome amplification is used to detect and identify microorganisms, assess response to therapy, and detect mutations associated with drug resistance. Nucleic acid amplification tests have been shown to be superior to conventional culture-based testing methods in many circumstances. However, the enthusiasm for the technology in clinical laboratories may be decreased by the practical considerations of cost, complexity of the technology, and lack of US Food and Drug Administration–approved tests. The impact of nucleic acid amplification tests on the diagnosis and management of patients with tuberculosis, enteroviral meningitis, and BK virus transplant nephropathy will be examined, with an emphasis on the potential for health care cost savings.

Nucleic acid amplification methods have greatly expanded the capabilities of clinical microbiology laboratories and have created new paradigms for the diagnosis and management of illness in patients with many infectious diseases. These tests have analytical sensitivities that are unmatched by other methods of analysis. They have also been instrumental in the discovery of previously unrecognized or undiscovered pathogens, including hepatitis C virus (HCV), Kaposi sarcoma–associated herpesvirus, Sin nombre virus, Bartonella henselae, Tropheryma whipplei, and Mycobacterium genavense. Nucleic acid amplification tests are commonly used to detect known agents that are difficult or impossible to grow in culture. These tests have become the new gold standards for the diagnosis of diseases caused by many different organisms, including HIV-1, HCV, cytomegalovirus, Bordetella pertussis, and Chlamydia trachomatis, and have created new opportunities for the laboratory to impact patient care.

The enthusiasm for the technology in clinical laboratories is often tempered by practical considerations. The reagents are expensive, and reimbursement for the tests may not entirely cover the costs. These tests are often technically complex and may supplement—rather than replace—traditional diagnostic methods, thereby creating more work for the laboratory. The diagnostic industry has not kept pace with the medical demand for these tests, and consequently, there are no US Food and Drug Administration (FDA)–approved tests for some applications that have become standards of care in many medical centers. The paucity of FDA-approved tests has limited the availability of many nucleic acid amplification tests to large referral centers and has led to problems with agreement between results obtained by laboratories using different in-house–developed tests.

Laboratory resources are not limitless. Given the concerns outlined above, it is important that we select the clinical applications of this technology wisely. In this article, how existing nucleic acid amplification tests impact diagnosis and patient management in pulmonary tuberculosis, enteroviral meningitis, and BK virus transplant nephropathy will be examined as examples, with a particular emphasis on the potential for health care cost savings.

PULMONARY TUBERCULOSIS

The current gold standard for the diagnosis of tuberculosis is culture. Traditional culture techniques for Mycobacterium tuberculosis using solid media require several weeks to 2 months to yield positive results. Enriched liquid culture media and
newer methods for monitoring these cultures for growth can provide earlier results, but often not within a clinically relevant time frame. Smear microscopy for acid-fast bacilli (AFB) is rapid, but insensitive: at best, only 50%–70% of patients with pulmonary tuberculosis have positive sputum smear results. As a consequence, antituberculosis therapy and respiratory isolation are typically initiated before laboratory confirmation of the diagnosis. This presents substantial problems for patient management, because the clinical features of tuberculosis are nonspecific.

The development of PCR and related nucleic amplification techniques in the late 1980s offered the promise to revolutionize the diagnosis of tuberculosis. One of the early FDA-approved diagnostic techniques based on this technology was for tuberculosis. Currently, 2 FDA-approved tests (AMTD2 [GenProbe] and Amplicor [Roche]) and a variety of user-developed methods are in use in clinical laboratories in the United States [1]. The major concerns about nucleic acid amplification tests for M. tuberculosis are their poor sensitivity with AFB smear–negative samples and their lack of availability in resource-poor situations, where the incidence of tuberculosis is often high. These tests supplement—rather than replace—culture, because of concerns about sensitivity with smear-negative samples and because a viable isolate is needed for drug susceptibility testing. Despite the widespread acceptance of nucleic acid amplification tests and the availability of FDA-approved diagnostic tests using this technology, little data are available on their clinical or economic impact.

Dowdy et al. [2] constructed a decision analysis model to evaluate the cost-effectiveness of the first version of the AMTD test to rapidly exclude pulmonary tuberculosis in patients with AFB smear–positive respiratory tract specimens. The costs associated with the AMTD test were compared with the averted costs of respiratory isolation and medication for patients with negative test results. The sensitivity (99.6%), specificity (99.7%), and AMTD inhibition rate for smear-positive specimens (0% for patients without tuberculosis and 2.3% for patients with tuberculosis) were estimated from literature reports. All costs, the annual number of specimens processed by the laboratory for mycobacteria (4600), the annual number of respiratory tract smear–positive patients (14), the proportion of smear-positive patients with tuberculosis (31.4%), and the time required to identify M. tuberculosis by AMTD and a culture-based method (median difference, 6 days), were locally determined at an urban hospital in the United States.

Under these conditions, the marginal costs of AMTD testing were estimated at $388 per smear-positive patient, or $494 for each case of early exclusion of tuberculosis determined on the basis of negative AMTD results. By comparison, the cost of respiratory isolation ($27.77 per day) and medications ($5.66 per day) averted by AMTD testing was estimated at $201 per early tuberculosis exclusion. Therefore, AMTD testing was not considered to be cost effective under these conditions.

Although AMTD testing was not cost effective in the base case scenario described above, Dowdy et al. [2] found that the estimates were highly sensitive to the relative prevalence of tuberculosis among smear-positive patients, the number of specimens processed annually, the marginal cost of the AMTD reagents, and the marginal daily costs of respiratory isolation. The cost effectiveness of AMTD testing by prevalence of tuberculosis among smear-positive patients, patient load, and isolation costs was estimated as a decision tool that could be used in determining whether this testing is cost effective in any clinical circumstance. The 2 most important factors driving cost effectiveness were high rates of other mycobacterial infections in smear-positive patients and high respiratory isolation costs.

An enhanced AMTD test (AMTD2) has been approved by the FDA for testing of both AFB smear–positive and AFB smear–negative respiratory specimens. Nucleic acid amplification tests may have the biggest impact on the management of patients with smear-negative specimens. Mazurek et al. [3] examined the clinical and economic impact of the AMTD2 test on the diagnosis of tuberculosis. In this prospective, unblinded, multicenter study, patients were randomized to AFB smear and culture with or without the AMTD2 test. There were a total of 399 eligible subjects at the 4 centers; a total of 40 of these eligible subjects received a clinical diagnosis of pulmonary tuberculosis. Of these, 38 had positive cultures. The culture methods included both rapid broth and solid media. The performance characteristics of the smear, the AMTD2 test, and culture were compared with the final clinical diagnosis. The study outcomes for subjects in the AMTD2 and no AMTD2 arms were days to initiation of appropriate antituberculosis therapy, days of unnecessary antituberculosis therapy, days of unnecessary isolation, days of hospitalization, number of invasive diagnostic procedures, median total costs for subjects with tuberculosis, median total costs for subjects without tuberculosis, time to initiation of contact investigations, and number of unnecessary contact investigations.

The sensitivity and specificity of the AFB smear, the AMTD2 test, and culture were 72.4% and 96.3%, 89.7% and 100%, and 86.2% and 100%, respectively, for the diagnosis of pulmonary tuberculosis. Although the AMTD2 test performed better than the AFB smear or culture for diagnosis of tuberculosis, no significant differences were found in any of the study end points between the AMTD2 and no AMTD2 arms. However, the power was not adequate to indicate equivalence. Subgroup analysis showed that HIV-infected subjects without tuberculosis in the AMTD2 arm were less likely to receive unnecessary treatment than similar patients with subjects in the no AMTD2 arm (P = .024), and they received unnecessary therapy for a shorter period of time (P = .024).
The accuracy of the AMTD2 test was greater than that of the AFB smear, but was similar to the accuracy of culture; however, the high AFB smear-positive rate (72.4%) may have limited the opportunity for the AMTD2 test to impact the diagnosis of tuberculosis in this study. Although no clinical or economic impact was documented, the AMTD2 test did provide early laboratory confirmation of tuberculosis in 90% of the subjects with tuberculosis and provided the opportunity for avoiding treatment in 8% of subjects suspected of having tuberculosis who were unnecessarily treated. The authors concluded that the AMTD2 test did not have a clinical or economic impact in this study except in HIV-infected patients.

It is clear from the above studies and the numerous published evaluations of nucleic acid amplification tests for *M. tuberculosis* that these tests provide an opportunity for early laboratory confirmation of pulmonary tuberculosis; however, the available data suggest that these tests have little measurable clinical or economic impact. The promise of molecular diagnostics to revolutionize the diagnosis of tuberculosis is still unfulfilled.

**ENTEROVIRAL MENINGITIS**

Enteroviruses are responsible for a wide variety of diseases in children and adults, including nonspecific febrile illnesses and meningitis [4]. Enteroviruses may cause up to 90% of cases of aseptic meningitis for which an etiology is identified. Occurring mainly in the summer and fall, enteroviral meningitis leads to a large number of hospitalizations of both children and adults. Enteroviral meningitis may be difficult to differentiate from partially treated bacterial meningitis because the CSF pleocytosis may have an early predominance of neutrophils. Many patients who have enteroviral meningitis are hospitalized and treated with parenteral antibiotics until the clinical situation improves and bacterial cultures of blood and CSF are negative after 48 h of incubation. CSF viral cultures have limited clinical utility in the management of cases because of poor sensitivity (65%–75%), a long turnaround time (3–7 days), and high cost [4].

Nucleic acid amplification tests for enterovirus RNA in blood and CSF have emerged as the new gold standard for diagnosis. These tests have better sensitivity than culture (90%–100%), results can be available within hours of specimen collection, and the costs are competitive with those of viral culture. Despite the enhanced performance characteristics and potential for improving the paradigms for diagnosis and patient management, there are no FDA-approved enterovirus RNA tests.

Numerous studies have been published in the past decade that model and document the clinical and economic impact of nucleic acid amplification testing for diagnosis of enteroviral meningitis in children. In one of the earliest studies, Marshall et al. [5] demonstrated the potential cost savings associated with the use of an RT-PCR test for enteroviruses in infants admitted to the hospital for “rule-out sepsis,” fever of unknown origin, or suspected meningitis when RT-PCR results were available within 24 h of admission. The use of the RT-PCR test demonstrated a 17%–35% savings in total health care costs, depending on how the positive test results were used in discharge planning.

Hamilton et al. [6] reviewed the charts of 125 patients with suspected enteroviral disease and found that the mean length of hospitalization was significantly shorter for patients who were enterovirus RNA-positive than for case control subjects. In a larger retrospective chart review, Ramers et al. [7] found that, in patients for whom enterovirus RT-PCR results were available before discharge, those with positive results underwent significantly fewer ancillary diagnostic tests, received parenteral antibiotics for a shorter amount of time, and had shorter hospital stays than those with negative test results.

A decision analysis model was developed by Nigrovic and Chang [8] to model the potential cost savings associated with testing CSF samples from infants with fever and the analysis of CSF pleocytosis for enterovirus RNA using RT-PCR. The model was based on receiving RT-PCR results within 24 h after admission. The model predicted 10% direct cost savings at a disease prevalence of 36.3% and 20% cost savings at a disease prevalence of 66.7%. In this model, significant direct cost savings were found, even assuming a low disease prevalence (with a break-even point for RT-PCR testing of only 6% prevalence). The prevalence of enteroviral meningitis can often exceed 50% during the summer months.

Robinson et al. [9] compared antibiotic use, length of hospital stay, and hospital charges among a group of patients with enteroviral meningitis whose positive enterovirus RT-PCR results were available within 24 h after specimen collection with a group of similar patients whose results were available >24 h after collection. Patients whose RT-PCR results were available within 24 h received antibiotics for 20 h less (*P* = .006) and incurred $2798 less in hospital charges (*P* = .001), compared with the patients whose results were available later. However, of these patients whose positive results were available within 24 h, those patients who were hospitalized did not receive significantly less antibiotic therapy or experience a shorter length of stay, but hospital charges were reduced by $2331 (*P* = .009). The reason admitted patients did not benefit from rapid RT-PCR results as much as did the entire study group was not clear to the authors, but it may have been the result of a higher level of concern that physicians have for hospitalized patients and a lack of prompt response by physicians to positive RT-PCR results.

Stellrecht et al. [10] examined the correlation between the turnaround time for enterovirus RT-PCR results and the length of hospital stay for a total of 1056 infants who were admitted to the hospital from 1998 to 2001. Shorter turnaround time was significantly correlated with decreased length of hospital
specimen showing cytopathic effect and viral inclusions with planted kidney leads to viruria and viremia. In cases of BKVN, active replication of the virus in the transallografts. Nephropathy occurs without any overt signs or symptoms except increasing serum creatinine concentrations. To 50% of patients who develop BKVN have lost their renal mycophenolate mofetil in combination [12]. Historically, up 1%–10% of renal transplant recipients. BKV nephropathy BK polyoma virus (BKV) is known to cause nephropathy in 1%–10% of renal transplant recipients. BKV nephropathy (BKVN) was first reported in 1995, coinciding with the widespread use of the immunosuppressive drugs tacrolimus and mycophenolate mofetil in combination [12]. Historically, up to 50% of patients who develop BKVN have lost their renal allografts. Nephropathy occurs without any overt signs or symptoms except increasing serum creatinine concentrations. In cases of BKVN, active replication of the virus in the transplanted kidney leads to viruria and viremia.

The gold standard for diagnosing BKVN is a renal biopsy specimen showing cytopathic effect and viral inclusions with positive immunohistochemical staining directed against a cross reactive SV40 large T antigen. However, a number of noninvasive diagnostic techniques have been employed for BKVN. Both viral culture and electron microscopy of urine are possible, but these techniques are impractical for routine clinical use because of technical limitations and cost. Urinary epithelial cells with viral inclusions, or “decoy cells,” are shed in all cases of BKVN and can be easily detected by Papanicolaou staining. Although this method is sensitive enough to diagnose BKVN, it is nonspecific, with a low positive predictive value.

Multiple reports have documented the use of PCR testing to detect BKV DNA in urine and plasma [12–15]. Although both tests are sensitive, plasma testing is much more specific and is more useful for monitoring virological responses to medication changes after diagnosis. Interdisciplinary recommendations for screening and monitoring kidney transplant recipients for BKV replication have recently been published [16].

We developed a fluorescent, real-time, 5′-exonuclease assay targeting the VP1 region of the BKV genome for use in our population of renal transplant recipients. Patients are routinely monitored for BK viremia using plasma samples obtained at regular intervals after transplantation or if there is a suspicion of BKVN. Our program has not lost a single renal allograft as a result of BKVN in the 3 years since our prospective monitoring program was implemented. Prospective monitoring with viral load tests provides the opportunity for earlier recognition of the disease by promoting early biopsy and earlier adjustment of immunosuppressive medications, which is currently the only effective intervention.

Historically, 2% of renal allografts were lost as a result of BKVN at our center. We estimated that viral load monitoring prevents the loss of 4 allografts per year as a result of BKVN (of the ~200 kidney transplantations performed each year). The cost of retransplantation at our center is ~$120,000 per patient, and the laboratory charges for viral load testing in patients who are prospectively monitored total $1640 per patient. These figures provided the basis for a rough estimate of the net cost benefit of BK viral load monitoring in renal transplant recipients. Assuming that each patient who lost an allograft to nephropathy received another transplant, we estimated a cost benefit of at least $760 per patient with viral monitoring. This estimate did not include dialysis or other costs associated with managing renal failure.

CONCLUSIONS

It is clear that nucleic acid amplification methods offer new opportunities for laboratory testing to improve the diagnosis and management of illness in patients with infectious diseases. However, the introduction of new diagnostic tests does not always lead to improved health outcomes. Because laboratory resources are not limitless and the technology still remains
relatively expensive, clinical applications should be carefully considered, and cost accounting should be performed globally.

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References