PCR-based Testing for Enterovirus Improves Clinical and Economic Outcomes in Children With Suspected Aseptic Meningitis

Aseptic meningitis is a common pediatric infection, affecting approximately 75,000 American children annually, with the vast majority of these cases (80% to 90%) caused by infection with an enterovirus. Because enteroviral meningitis has a benign clinical course and is managed symptomatically, typically without hospital-administered intravenous antibiotics, its diagnostic distinction from clinically indistinguishable bacterial meningitis (requiring expensive antibiotics) is critical. Failure to promptly identify enterovirus as the etiologic agent of meningitis typically results in an extensive (and expensive) hospital-based diagnostic evaluation, much of which could be alleviated with a rapid, sensitive enteroviral diagnostic test. Because cerebrospinal fluid (CSF) viral culture detection of this organism is time-consuming (requiring 3 to 10 days) and insensitive, it is of little practical utility in deciding which patients require extended hospitalizations and antibiotic therapy. In comparison, a recent outcomes-based study of children with suspected aseptic meningitis has shown that a rapid enteroviral PCR diagnostic test is not only analytically superior to viral culture detection methods, but its routine use also leads to significant reductions in the utilization of expensive hospital resources. In particular, Ramers et al. [1] have shown a 50% CSF PCR-positivity rate among 276 consecutive hospitalized children with suspected enteroviral meningitis. In a follow-up outcomes analysis, these investigators showed that children with positive CSF enteroviral PCR results, as compared to those with negative PCR results, had significantly fewer ancillary tests performed, received less intravenous antibiotics, and, perhaps most importantly, had earlier hospital discharges resulting in shorter hospital stays. Although a detailed economic analysis was not performed, the reduced use of these expensive hospital resources (diagnostic tests, antibiotics, and inpatient days) would likely result in not only significant cost savings, but it would also allow the sick child to recuperate predominantly in the familiar home setting rather than the frightening hospital setting. The clinical, economic, and psychosocial gains of a rapid enteroviral PCR test would, of course, be lost if the laboratory’s turnaround time was longer than the clinical decision-making timeline. The rapid 26- to 42-hour median test turnaround times reported by Ramers et al. (for PCR-positive vs PCR-negative patients) could only be accomplished, for example, by running PCR test batches on a frequent schedule of six times per week that likely resulted in less than full-batch capacities and thus increased direct test costs. Smaller hospitals and/or those without PCR-based expertise would be unable to offer such frequent testing. Despite these limitations, this study is one of the first to unbiasedly document what we in the molecular diagnostic community have been preaching for quite some time—that the prudent use of expertly performed specialized diagnostic tests (even expensive ones) will result not only in better medical outcomes, but will also, by reducing subsequent unnecessary interventions, result in lower total healthcare costs.

Proficiency Survey Reveals High Error Rates for Diagnostic Genetic Testing

A recent report from a European quality control program suggests an unexpectedly high diagnostic error rate among laboratories performing cystic fibrosis (CF) genetic testing [2]. In particular, among the approximately 150 participating laboratories testing 18 blinded CF DNAs (six annually) sent by the European Concerted Action on Cystic Fibrosis, the rate of incorrectly assigned CF allele designa-
tions ranged from 7.7% (during the first year of the survey) to 3.8% (during the survey’s third and final year). Of the 114 laboratories participating in each of the surveys, only 55 (48%) were found to have made no CF genotyping errors over the entire 3-year period. Moreover, in each of the annual proficiency surveys, more than 20% of the participating laboratories failed to correctly type at least one of the six DNA challenges. Not unexpectedly, the rate of genotyping errors seemed to be highest in those laboratories with the lowest diagnostic sample volumes. A similar relationship between genetic testing laboratories’ “quality assurance score” and their testing volumes had been previously documented by a survey of North American laboratory directors [3]. Another surprising finding from the more recent European report was the realization that, despite the progressive trend over time toward the use of commercially available (rather than in-house-derived) genetic testing reagents, the use of these diagnostic testing kits did not, in itself, ensure a high level of genotypic accuracy. On a more optimistic note, although the overall analytical error rates for the CF genetic test were considerably higher than expected, the progressively decreasing trend in error rates (from 7.7% to 3.8% in 3 years) suggests that the committed quality control efforts of the molecular genetic testing community may be having a positive impact on the quality assurance of this and other highly complex molecular diagnostic assays.

**Rapid, Reliable Detection of Intrapartum Group B Streptococci by PCR**

Group B streptococci are the leading cause of life-threatening infections in newborns, the early-onset type being invariably caused by contacting or aspirating an infected maternal genital tract during delivery. A large 15% to 40% fraction of the female population is colonized by group B strep. Strategies to reduce neonatal transmission include antibiotic prophylaxis in women with positive screening cultures in the third trimester (35 to 37 weeks), or in women considered “high risk” for group B strep neonatal transmission by virtue of intrapartum fever, imminent preterm delivery, or premature membrane rupture. The clinical utility of third-trimester screening cultures is somewhat limited by its inability to predict late-onset maternal colonization (at delivery) and by false-negative culture results due to the complex *in vitro* growth requirements of group B strep. The alternative “risk assessment” approach is even more problematic, because only approximately 20% of the at-risk women getting antibiotic prophylaxis are actual group B strep carriers.

To overcome these significant limitations, the Centers for Disease Control and Prevention has called for the development of rapid, sensitive, easy-to-use alternative testing methods for group B strep detection in pregnant women. A rapid PCR method for detection of group B strep from vaginal, anal, or combined vaginal-anal swabs has recently been shown to be both sensitive and specific for the intrapartum detection of this organism both before and after membrane rupture [4]. In particular, Bergeron et al. [4] have shown that the intrapartum detection of group B strep from a combined vaginal-anal swab specimen using a PCR method was 97% sensitive and 100% specific as compared with a “gold standard” culture method. The PCR assays detailed by these investigators included both a conventional gel-based detection system (with claims of a 100-minute turnaround time) and a more rapid fluorometric real-time PCR detection system (with claims of a 30- to 45-minute turnaround time). Both PCR assays were able to detect the same 32 (of 33) culture-positive specimens. The only discrepant sample was a specimen harvested after membrane rupture from a woman with negative culture and PCR results from before membrane rupture. Although these PCR assays offer the theoretical promise of a more rapid and reliable detection of this clinically relevant pathogen, the stated time-to-results of 30 to 100 minutes is likely optimistic given the real-world pressures on clinical laboratories to reduce test costs—often achieved by batched test runs and their associated longer turnaround times. In routine clinical practice, the implementation of a rapid diagnostic test for obstetric patients at the time of delivery would, of course, also demand round-the-clock availability of highly trained technical and interpretive staff, the costs of which would be significant. A worthy goal for the clinical molecular diagnostic community is to collaboratively overcome these and other nonmedical administrative hurdles to deliver analytically and tempo-