Preface

Advances in Clinical Laboratory Testing for Neurologic Disorders

The number of cells in the human brain is thought to exceed the number of stars in our galaxy. Due to the tremendous scale and complexity of how brain cells interact, many factors can predispose patients to develop neurologic disease. Fortunately over the past ten years, there has been significant progress in our understanding of how to diagnose and treat patients with these complex disorders.

Identification of the genetic changes underlying several major neurologic diseases has been a significant driver of this progress. For example, diagnosis of spinal muscular atrophy (SMA) is multifaceted, characterized by mutations or deletions in the *SMN1* gene that can be accompanied with changes in the copy number of a second gene named *SMN2*. Together, these alterations determine the phenotypic severity of SMA. Unfortunately, the sequence similarity of these two homologous genes makes carrier screening and patient diagnosis challenging. Over the past five years, the Food and Drug Administration has approved two new treatments that may be curative. Selecting appropriate testing methodologies and correctly interpreting the results are of utmost importance for these patients and their families because accurately diagnosing this disease at an early age can profoundly impact clinical prognosis.

Another major genetic advance in this area is our understanding that amyotrophic lateral sclerosis and frontotemporal dementia can be linked with a hexanucleotide repeat expansion in the *C9ORF72* gene, and the length of this repeat is correlated with disease expression. Since the pathogenic allele exhibits somatic instability and can contain hundreds to thousands of guanine and cytosine repeats, the sequencing methodology and target tissue used for patient diagnosis must be carefully considered. Achieving accuracy and consistency in diagnostic methods is of paramount importance for counseling patients who may harbor this repeat expansion and for clinical trials targeting this gene.

Immunologic testing for neurologic diseases is another discipline that is growing at a rapid pace. The discovery of autoantibodies that cause encephalitis and paraneoplastic syndromes has been a major advance in terms of both diagnosis and treatment. Laboratory testing for these syndromes uses a range of analytic techniques, including enzyme-linked immunoassays, radioimmunoprecipitation assays, western blots, and cell-based immunofluorescence performed at different titers of patient serum. These tests are not trivial to develop and can be complex to interpret. Clear identification of pathogenic antibodies within the appropriate clinical context can direct cancer screening in patients with paraneoplastic syndromes and can also facilitate the selection of an appropriate treatment protocol for patients with encephalitis.

Another emerging frontier in laboratory testing for neurodegenerative disorders has stemmed from the discovery of how prion-mediated diseases are transmitted. It has been shown that conformationally altered prion protein can propagate disease by inducing structural change in the normal cellular form of this protein. This finding has

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been applied to diagnostics using *ex vivo* amplification of pathogenic, misfolded proteins from clinical samples to detect abnormal prion protein. Similar analytic techniques have been applied to detect synuclein, beta-amyloid, and tau from patient samples, because conformationally altered forms of these proteins are found in Parkinson and Alzheimer disease. It remains to be seen whether these methodologies can be standardized, widely replicated, and incorporated into the workflow of immunoassay and nucleic acid tests that form the backbone of clinical laboratory testing.

It has been an honor and a wonderful learning experience to serve as guest editor for this issue of *Clinics in Laboratory Medicine*, and I greatly appreciate the expertise, time, and dedication of our authors as well as the editorial staff at Elsevier. I hope that this issue will be insightful for our readers by highlighting the progress that has been made in the area of neurologic disease testing and clarifying the work that remains ahead.

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