

# Contents

**Preface: Advances in Clinical Laboratory Testing for Neurologic Disorders** ix

A. Zara Herskovits

**Optimizing Genetic Diagnosis of Neurodevelopmental Disorders in the Clinical Setting** 231

David Joshua Michelson and Robin Dawn Clark

Progress in medical genetics has changed the practice of medicine in general and child neurology in particular. A genetic diagnosis has become critically important in determining optimal management of many neurodevelopmental disorders, making genetic testing a routine consideration of patient care in outpatient and inpatient settings. Today's child neurologists should be familiar with various genetic testing modalities and their appropriate use. Molecular genetic testing of children with unexplained developmental delays and/or congenital anomalies has a 20% to 30% chance of identifying a causative etiology. Newer methods have made genetic testing more widely available and sensitive but also more likely to produce ambiguous results.

**Proteopathic Seed Amplification Assays for Neurodegenerative Disorders** 257

Natália do Carmo Ferreira and Byron Caughey

The need for etiological biomarkers for neurodegenerative diseases involving protein aggregation has prompted development of ultrasensitive cellular and cell-free assays based on the prion-like seeding capacity of such aggregates. Among them, prion RT-QuIC assays allow accurate antemortem Creutzfeldt-Jakob disease diagnosis using cerebrospinal fluid and nasal brushings. Analogous assays for synucleinopathies (e.g., Parkinson disease and dementia with Lewy bodies) provide unprecedented diagnostic sensitivity using cerebrospinal fluid. Biosensor cell and tau RT-QuIC assays can detect and discriminate tau aggregates associated with multiple tauopathies (e.g., Alzheimer disease and frontotemporal degeneration). An expanding panel of seed amplification assays should improve diagnostics and therapeutics development.

**Genetic Testing for Amyotrophic Lateral Sclerosis and Frontotemporal Dementia: Impact on Clinical Management** 271

Jennifer Roggenbuck and Jamie C. Fong

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are devastating neurodegenerative disorders that share clinical, pathologic, and genetic features. Persons and families affected by these conditions frequently question why they developed the disease, the expected disease course, treatment options, and the likelihood that family members will be affected. Genetic testing has the potential to answer these important questions. Despite the progress in gene discovery, the offer of genetic testing is not yet "standard of care" in ALS and FTD clinics. The authors

review the current genetic landscape and present recommendations for the laboratory genetic evaluation of persons with these conditions.

**Diagnostic and Prognostic Laboratory Testing for Alzheimer Disease**

**289**

Zachary Winder, Donna Wilcock, and Gregory A. Jicha

This article focuses on current clinical laboratory testing to diagnose Alzheimer disease and monitor its progression throughout its disease course. Several clinically available tests focus on analysis of amyloid and tau levels in cerebrospinal fluid as well as autosomal dominant and risk factor genes. Although the current armament of clinical laboratory testing is limited by invasiveness of cerebrospinal fluid collection, rarity of autosomal dominant genetic mutations, and uncertainties of risk inherent in nonpenetrant genes, the field is poised to advance the clinical repertoire of laboratory diagnostic testing.

**Confounders in the Interpretation of Paraneoplastic and Neuronal Autoantibody Panels**

**305**

Naveen George, Neel Fotedar, and Hesham Abboud

The recent discovery of several neuronal autoantibodies linked to neurologic syndromes that are fully or partially responsive to immunosuppressive therapy has revolutionized neuroimmunology and expanded the scope of classical paraneoplastic and antibody-related syndromes. A great deal of understanding of the techniques of neuronal antibody testing, the sensitivity and specificity of serum and cerebrospinal fluid sampling, and the value of the specific type and titer of each antibody is imperative. This article provides an overview of neuronal antibody and paraneoplastic panel testing with emphasis on how to differentiate clinically relevant from clinically irrelevant results and the downstream implications of those results.

**Reference Laboratory Testing for Neurologic Disorders**

**317**

A. Zara Herskovits and Loren J. Joseph

Laboratory testing plays a critical role in the diagnosis and monitoring of patients with neurologic disorders. Although common tests are often performed in a central hospital laboratory, an increasing number of essential but esoteric tests are performed at reference laboratories or other outside health care facilities. In this article, we analyze recent trends in neurologic disease testing within the overall context of reference laboratory testing and discuss strategies to facilitate the provision of high-quality, cost-effective laboratory services.

**The Development of New Diagnostic Tests for Neurologic Disorders in the Commercial Laboratory Environment**

**331**

Iswariya Venkataraman and Stanley J. Naides

Development of new diagnostic tests in a commercial laboratory for neurologic disorders is challenging. Development occurs in a highly regulated environment. Relevant research infrastructure may not be readily available in-house and may require outsourcing with additional management and

costs. Clinically characterized specimens for validation of biomarkers for esoteric diseases may be difficult to acquire, and market size may be difficult to predict. More common diseases with heterogeneous subsets may require better clinical definition. Absence of guidelines may delay health provider acceptance of novel testing. Regulatory agency approval and categorization of tests affects validation requirements and impacts market acceptance and reimbursement.

**Something's Lost and Something's Gained: Seeing Reference Laboratory Quality from Both Sides, Now** **341**

Yael K. Heher

Growing regulatory burdens, payment model changes, and increased complexity in laboratory medicine have contributed to an increased reliance on reference laboratories. Although reference laboratories often offer rapid, low cost, high quality testing, outsourcing laboratory tests can create quality and patient safety vulnerabilities particularly in the pre-analytic and post-analytic phases of the test cycle. Disconnects in governance, policy, and information technology between the reference laboratory and the referring provider conspire to increase risk. Laboratory leaders seeking to reduce risk and improve quality must ensure clear and collaborative oversight, monitor meaningful quality metrics, and integrate feedback from ordering providers.

**Diagnostic Testing for Patients with Spinal Muscular Atrophy** **357**

John F. Brandsema, Brianna N. Gross, and Susan E. Matesanz

Diagnostic genetic testing for spinal muscular atrophy is key in establishing early diagnosis for affected individuals. Prenatal carrier testing of parents with subsequent testing of the fetus for homozygous SMN1 gene deletion in those at risk of this autosomal recessive disorder as well as newborn screening can identify the vast majority of affected individuals before the onset of symptoms. Patients presenting symptomatically must be genetically confirmed as soon as possible because targeted treatments are now available that profoundly impact symptoms and improve quality of life.

**Cerebrospinal Fluid Testing for Multiple Sclerosis** **369**

Joshua F. Goldsmith and A. Zara Herskovits

Multiple sclerosis is one of the most common autoimmune diseases affecting the central nervous system. Current guidelines characterize multiple sclerosis and related conditions based on clinical, imaging, and body fluid markers. In this review, we describe how laboratory analysis of cerebrospinal fluid is currently performed and discuss new approaches under development for multiple sclerosis diagnostics.