Position Statement
American Association of Neuromuscular & Electrodiagnostic Medicine

THE UTILITY OF GENETIC TESTING IN NEUROMUSCULAR DISEASE

Introduction

The American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) has developed a position statement regarding the utility of genetic testing in neuromuscular (NM) disease.[1] This position statement was prompted by inquiries from members and insurance providers regarding whether genetic testing for NM diseases is valuable and beneficial in light of the costs of testing.

The aim of this position statement is to provide a recommendation from experts at the AANEM on the clinical utility of genetic testing and is not meant to recommend or endorse any specific genetic testing methodology or algorithm. Many resources exist for physicians to help guide appropriate genetic testing in NM diseases.[2] There remains a role for single gene testing in cases with characteristic phenotypes in addition to larger gene panels or other techniques such as whole exome sequencing or whole genome sequencing. Features to consider when deciding on genetic testing include the pattern of inheritance, pattern of weakness, associated clinical features or electrophysiological and pathological findings. Genetic testing is now readily available for many NM diseases and should not be considered an unusual test only for research purposes. Testing should be ordered from accredited laboratories, such as those that have received Clinical Laboratory Improvement Amendments (CLIA) certification in the United States.

It is the position of the AANEM that genetic testing plays a vital role in the care of patients with inherited neuromuscular conditions by:

(1) Identifying patients with treatable inherited neuromuscular diseases.
(2) Avoiding harm related to delayed diagnosis, misdiagnosis, and unnecessary testing.
(3) Identifying patients who need monitoring of comorbidities related to their genetic condition.
(4) Providing guidance for family planning.
(5) Identifying patients eligible for research studies including clinical trials that may lead to new disease-modifying therapies.
(6) Reducing unnecessary healthcare expenditures by avoiding prolonged diagnostic evaluations, and unnecessary procedures and treatments.

(1) Disease-modifying therapies are available

One of the chief arguments for deferring genetic testing has been that no treatment existed to alter the clinical course. This argument is outdated. There are now multiple approved disease-modifying therapies for inherited neuromuscular conditions, including but not limited to spinal muscular atrophy, Duchenne muscular dystrophy, Pompe disease, Friedreich ataxia, transthyretin amyloidosis, and SOD-related familial amyotrophic lateral sclerosis (ALS).[3] These include gene therapies, RNA-targeting treatments, and enzyme replacement. Many of these treatments have been demonstrated to significantly alter the course of the disease and, in some cases, are life-saving.[4] Delay in treatment of these diseases results in further progression of disease and related comorbidities, making a timely diagnosis crucial.

(2) Harms related to delayed diagnosis, misdiagnosis, and unnecessary testing

Patients and family members without a confirmed molecular diagnosis may undergo unnecessary testing, including invasive procedures such as muscle or nerve biopsies, sometime repeatedly during the diagnostic process. The procedures carry a small but recognized morbidity including anesthetic risks, bleeding, infection, permanent numbness and chronic pain., Advances in genetic testing have changed the role of invasive testing such as muscle biopsy; patients with a phenotype typical of an inherited disorder should undergo genetic testing as the first-line diagnostic modality.[2]

Patients with undiagnosed NM disease may also receive empiric treatment with immunosuppressive or immunomodulating medications, including corticosteroids and intravenous immunoglobulin (IVIg), for a suspected treatment-responsive condition.[5] These medications can cause serious adverse effects, particularly with corticosteroid use.[6, 7] Establishing a molecular diagnosis may help avoid unnecessary treatment and its associated risks.

Several reports have acknowledged long delays (5 to 7 years or longer, depending on the country and methodology) in

arriving at a diagnosis for rare genetic diseases. During this period, patients and family members report significant emotional impacts, such as psychosocial stress, depression, and lower health-related quality of life. A molecular diagnosis provides closure and help patients and families to access resources from disease-specific support groups.[8]

(3) Surveillance and management of comorbidities

Many inherited NM diseases are multi-systemic, involving cardiac, respiratory, and other organ systems. In some diseases, sudden cardiac death is a serious but potentially treatable and avoidable comorbidity. By arriving at a molecular diagnosis, the clinician can arrange appropriate and potentially life-saving surveillance or referrals (for example to a cardiologist for investigation and consideration of an implantation of a defibrillator-pacemaker in a patient with limb girdle muscular dystrophy (LGMD)1B.[9] In other cases, routine screening for treatable comorbidities that could improve quality of life would be prompted by the specific diagnosis, such as screening for cataracts and diabetes in a patient with myotonic dystrophy. In addition, many of these diseases are associated with respiratory weakness, and identifying which patients need to be screened for asymptomatic respiratory insufficiency is crucial to prevent morbidity and mortality from respiratory failure.[10]

(4) Family Planning and Early Diagnosis

There is clinical utility to family members of knowing about an inherited disorder, since the specific genetic diagnosis helps to predict the pattern of inheritance. This information is critical for genetic counseling, specifically informing family planning discussions, as well as discussions around prenatal diagnosis or early diagnosis of asymptomatic family members.[11] Without a genetic diagnosis, physicians or genetic counsellors cannot adequately educate patients or predict risks in a manner that helps guide family planning or diagnostic decisions.

(5) Participation in Research, Clinical Trials and Patient Registries

Patients without a definite genetic diagnosis will be unable to participate in research studies including clinical trials which may lead to approved disease-modifying therapies. They would also be unable to participate in patient registries that are vital for better understanding the longitudinal course, clinical features, and progression of NM disease.

(6) Cost-effectiveness

Genetic testing may help reduce unnecessary healthcare expenditures by limiting the prolonged diagnostic evaluation associated with undiagnosed inherited NM disease. Without a confirmed molecular diagnosis, patients may undergo repeated muscle or nerve biopsies, nerve or muscle magnetic resonance imaging (MRI), electrodiagnostic studies, and blood or cerebrospinal fluid testing. Identifying the causative genetic variant in an affected family member can also guide targeted testing of relatives and may avoid additional diagnostic evaluations for other disorders.

A molecular diagnosis may also help avoid expenditures associated with unnecessary empiric treatment, including corticosteroids and IVIg, which have been associated with substantial costs. [6,7]

By helping clinicians select appropriate testing and management and avoid unnecessary procedures and treatments, genetic testing supports efficient, safe, and patient-centered care, consistent with the Institute of Medicine's quality domains.

Summary

The AANEM believes that genetic testing and arriving at a specific molecular diagnosis is critical to providing high quality and cost-effective care to NM patients. Many recommendations and guidelines exist to direct the rational selection of appropriate genetic testing. The cost of testing should not be a deterrent, since there are important clinical, safety, psychosocial, and research benefits to genetic testing in NM disease.

References

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