Position Statement

American Association of Neuromuscular & Electrodiagnostic Medicine

THE UTILITY OF GENETIC TESTING IN NEUROMUSCULAR DISEASE:

A Consensus From the AANEM on the Clinical Usefulness of Genetic Testing in the Diagnosis of Neuromuscular Disease

Introduction

The American Association of Neuromuscular &Electrodiagnostic Medicine (AANEM) has developed the following position statement regarding the utility of genetic testing in neuromuscular (NM) disease. 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. There remains a role for single gene testing in cases with characteristic phenotypes, in addition to larger gene panels or other techniques like whole exome 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.[1-4] 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 diagnosis, appropriate investigation, and monitoring of NM for several reasons including that they can 1) be cost effective by avoiding potential harm, 2) help with disease management, 3) improve the psychological impact on patients and family members by confirming the diagnosis, 4) assist with family planning, and 5) allow patients to participate in clinical trials and registries.

Cost-effectiveness and Avoiding Potential Harm

Presently, there is a major focus on improving the quality and cost-effectiveness of healthcare. Genetic testing contributes to the delivery of high quality patient care, as defined by the Institute of Medicine quality domains, by facilitating the provision of efficient, safe and patient-centered care.[5]

Due to ongoing diagnostic uncertainty, patients and family members without a confirmed molecular diagnosis may undergo unnecessary and costly testing, including invasive procedures such as muscle or nerve biopsies, which carry a small but recognized morbidity. These risks include anesthetic risks, bleeding, infection, permanent numbness and chronic pain. In addition, other testing may be pursued, including nerve or muscle imaging with magnetic resonance imaging (MRI), or costly blood and

cerebrospinal fluid testing. Additionally, by determining the proband (affected individual) in one family member, this may avoid additional testing of other family members for other disorders.

Patients with undiagnosed NM disease may also be treated empirically with immunosuppressive or immunomodulating medications looking for a treatment-responsive condition. Such medications include corticosteroids and intravenous immunoglobulin (IVIg) among others, which carry the potential for multiple serious side effects (particularly in the case of corticosteroids), and have been shown to be highly costly in multiple studies.[6-7]

Surveillance and Management

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.[1,8] 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 dystryophy (LGMD)1B.[8] 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 or diabetes in a patient with myotonic dystrophy. In rare situations, confirming a molecular diagnosis may lead to changes in medical therapy.[8]

Confirming the Diagnosis (Psychosocial Impact for the Patient and Family)

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.[9] During this period, patients and family members report significant emotional impacts, such as psychosocial stress, depression, and lower health-related quality of life.[9-11] Arriving at a molecular diagnosis provides closure, and allows the patient or their family to seek resources from disease-specific support groups. There is also a positive impact for the physician, who no longer has to contend with diagnostic uncertainty, or the worry of missing an acquired or treatable condition.

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[8]. 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.

Participation in Research, Clinical Trials and Patient Registries

Up to this point, one of the chief arguments for deferring genetic testing was that no treatment existed to alter the clinical course. This may be changing, as new treatments are being investigated or actively undergoing clinical trials.[12,13] Patients without a definite genetic diagnosis will be unable to participate in clinical trials, and subsequently may never be offered future approved therapies. Patient registries are another vital tool for better understanding the longitudinal course, clinical features, and progression of NM disease, but patients cannot be included in many registries without confirmed genetic diagnoses.

Summary

The AANEM believes that genetic testing and arriving at a specific molecular diagnosis is critical to providing high quality 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.

Approved by the American Association of Neuromuscular & Electrodiagnostic Medicine: April 2016.

References

1 Narayanaswami P, Weiss M, Selcen D, *et al.* Evidence-based guideline summary: Diagnosis and treatment of limb-girdle and distal dystrophies. *Neurology* 2014;83:1453–63. doi:10.1212/WNL.0000000000000892

2 Kang PB, Morrison L, Iannaccone ST, *et al.* Evidence-based guideline summary: Evaluation, diagnosis, and management of congenital muscular dystrophy. *Neurology* 2015;84:1369–78. doi:10.1212/WNL.0000000000001416

3 Tawil R, Kissel JT, Heatwole C, *et al.* Evidence-based guideline summary: Evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy. *Neurology* 2015;85:357–64. doi:10.1212/WNL.0000000000001783

4 Klein CJ, Duan X, Shy ME. Inherited neuropathies: Clinical overview and update. *Muscle and Nerve* 2013**;**48:604–22. doi:10.1002/mus.23775

5 Committee on Quality of Health Care in America I of M. Crossing the Quality Chasm: A New Health System for the 21st Century. In: *Crossing the Quality Chasm: A New Health System for the 21st Century*. 2001. 61–88.

6 Furlan JC, Barth D, Barnett C, *et al.* Cost-minimization analysis comparing intravenous immunoglobulin with plasma exchange in the management of patients with myasthenia gravis. *Muscle Nerve* Published Online First: 2015. doi:10.1002/mus.24960

7 Guptill JT, Sharma BK, Marano A, *et al.* Estimated cost of treating myasthenia gravis in an insured U.S. population. *Muscle and Nerve* 2012;45:363–6. doi:10.1002/mus.22327

8 Nolan D, Carlson M. Whole Exome Sequencing in Pediatric Neurology Patients: Clinical Implications and Estimated Cost Analysis. Published Online First: 2016. doi:10.1177/0883073815627880

9 Department of Health, UK Government. The UK Strategy for Rare Diseases. 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/260562/UK_Strategy_for_Rare_Diseases.pdf

10 Shire Human Genetic Therapies. Rare Disease Impact Report: Insights from patients and the medical community. 2013. www.geneticalliance.org.ul/docs/e-updates/rare-disease-impact-report.pdf

11 ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genet Med* 2015;17:505–7. doi:10.1038/gim.2015.41

12 Mendell JR, Rodino-Klapac LR, Sahenk Z, *et al.* Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol* 2013;74:637–47. doi:10.1002/ana.23982

13 Al-Zaidy S, Rodino-Klapac L, Mendell JR. Gene therapy for muscular dystrophy: Moving the field forward. *Pediatr Neurol* 2014;51:607–18. doi:10.1016/j.pediatrneurol.2014.08.002