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Q&A Summary

Genetic Testing and Treatment: Part 1, Neuromuscular Diseases

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Presenter: Peter B. Kang, MD, FAAN, FAAP; child neurologist and neuromuscular specialist; Gainesville, Florida

Available On Demand:
optumhealtheducation.com/neuromuscular-diseases-2020

1) Can you provide resources to help identify which current procedural terminology (CPT) code should be used for a particular test?
   - Many of the commercial genetic test companies list CPT codes on their websites. If the company you are currently using does not supply this information on their website, it would be worth looking around for one that does.

2) What is your best prediction on how much longer you think it will be before gene therapy is perfected and more widely used for various inherited neuropathies?
   - Gene therapy using viral vectors such as adeno-associated virus (AAV) is most advanced for recessive diseases, with spinal muscular atrophy (SMA) being a prime example, as the goal is to replace a gene that is missing entirely. Some of the more common inherited neuropathies such as Charcot-Marie-Tooth disease are typically dominant, with a gene dosage problem that may be more complex to solve. There were two exciting articles published recently in the *New England Journal of Medicine* that described two molecular approaches that show promise in treating cases of amyotrophic lateral sclerosis related to *SOD1* mutations, which are dominantly inherited; one of the approaches involved gene therapy. I expect that gene therapy for inherited neuropathies is feasible and promising but will take a while before coming to fruition.

3) What percentage of electromyographies (EMGs) have false negatives? Are there any conditions associated with false negative EMGs?
   - The sensitivity rates of EMGs vary depending on the chief complaint and what disease category is being queried. EMGs are very sensitive for detecting large-fiber neuropathies, both axonal and demyelinating. They are also reasonably sensitive for the detection of motor neuron diseases. They are less sensitive for detecting disorders of the neuromuscular junction (such as myasthenia gravis) and primary muscle diseases (such as muscular dystrophy). The detection rate is also highly dependent on whether sufficient nerves and muscles are tested for a particular diagnostic question. What counts as sufficient varies by the type of disease being queried. The completeness of the examination may be limited by certain circumstances, especially in the pediatric population, as well as the comfort level of the examiner for certain populations, such as children. It is difficult to give an

overall number as circumstances can vary considerably from patient to patient. It is important to remember that EMG can be a very useful and well-tolerated test in the right circumstances.

4) Given that whole-genome sequencing (WGS) and whole-exome sequencing (WES) are next-generation sequencing and are considered the best genetic testing methods, how can families meet the cost considering they are expensive? Can you provide information about the insurance coverage?
   - WGS and WES are important tools in genetic diagnosis. However, they may not always be the best tests to send for suspected inherited neuromuscular diseases. Some of the more common neuromuscular disorders are associated with structural variants that may not always be easily detected on WGS or WES. These include Charcot-Marie-Tooth disease type 1A and facioscapulohumeral muscular dystrophy (FSHD).

5) Any thoughts on epigenetic factors?
   - Epigenetic changes could be a major contributor to inherited neuromuscular diseases. They are already known to play a role in FSHD. Future research will help determine to what degree such changes can impact these diseases.

6) Can you provide information on hereditary spastic paralysis (HSP)?
   - HSP is an important category of neurogenetic diseases. It is sometimes considered a neuromuscular disease and sometimes a more general neurogenetic disease, thus it was not included in the main material for this presentation. It should be considered as a possibility when there is increased muscle tone and motor difficulties, primarily in the lower extremities. Patients with HSP are sometimes initially thought to have a tethered spinal cord and/or cerebral palsy, and it is important to evaluate for these other diagnoses depending on the clinical circumstances. Genetic testing is available, but a negative genetic test does not exclude this diagnosis.

7) How does one find a genetic counselor for adult mitochondrial disease?
   - For patients, some multidisciplinary neuromuscular and mitochondrial disease clinics have genetic counselors embedded in those clinics. If this is not available near you, the Clinical Genetics Department at a nearby comprehensive medical center and/or academic health center should be able to provide guidance on how to access this important resource.

8) Can you provide suggestions for treatment of small-fiber neuropathy?
   - If there is a clear underlying condition such as diabetes or a genetic disorder, addressing the underlying condition with any available therapies would help. Symptoms of small-fiber neuropathy can respond to various pharmacologic and nonpharmacologic therapies depending on the individual circumstances.

9) Is it clinically appropriate to use prednisone for Duchenne muscular dystrophy (DMD) vs deflazacort, which appears to have a better safety profile for long-term use?
   - Prednisone and deflazacort are both standard corticosteroids used for DMD, and both have slightly differing side-effect profiles. Deflazacort is the only one that is Food and Drug Administration (FDA) approved, but prednisone has been used for decades in these patients in the US. Prednisone is certainly a reasonable choice for certain patients, as long as the families are counseled on their options and other relevant issues such as side-effect profiles.

10) Where do you see risdiplam falling into therapy for SMA?
   - Risdiplam is a small molecule oral therapy that is undergoing human clinical trials. It is not currently approved by the FDA but may be in the future. As it is not approved, I cannot comment on its safety or efficacy at this time. If it is approved in the future, it may play an important role in SMA therapy as it would be the only oral medication approved for this disease.

11) How can you determine the difference between SMA type 1 and type 2 when the diagnosis is made in a newborn?
   - The distinction is difficult to make for some newborns. *SMN2* copy number on genetic testing can help to some extent but is not definitive, as the types are defined by motor milestones. Severe hypotonia and weakness, with early-onset feeding and respiratory difficulties, would suggest that the infant most likely has type 1, but such assessments should be made by pediatric neurologists who are experienced with evaluating such infants.

12) Is there any new or recommended treatment for inflammatory myopathy?
   - Therapy for inflammatory myopathy may be complicated, as traditional medications for this disease, such as corticosteroids, are accompanied by numerous chronic side effects. Steroid-sparing drugs may be options for some patients. In recent years, some patients have been observed to respond to monoclonal antibody therapies such as rituximab, and other biologic drugs (as opposed to small molecule traditional drugs) are under development. However, all of these therapies, including monoclonal antibodies and other biologic therapies, may be accompanied by significant side effects; therefore, a thorough discussion with a physician experienced in these matters is warranted before embarking on a course of therapy.

13) Has there been any progress in identifying genetic factors and/or testing for autism?
   - Indeed, there has been quite a bit of progress in both identifying genetic factors and for testing for autism. Here are some weblinks that you may find useful.
     - Autism Speaks: https://www.autismspeaks.org/science-blog

- American Academy of Pediatrics, Clinical Report, January 2020: https://pediatrics.aappublications.org/content/145/1/e20193447; https://pediatrics.aappublications.org/content/145/1/e20193448
- CDC: https://www.cdc.gov/ncbddd/autism/index.html
- And, in 2018, we presented a series on autism. Specifically, this one (which is free, recorded and still available for CEUs) is about autism spectrum disorder and genetics: https://www.optumhealtheducation.com/pediatrics/autism-part-III-2018.

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