

Genetic Testing in Neuromuscular Disease: Practical Considerations for Clinical Care Teams

A
Resource
for
Clinicians

Background

- In cases of suspected neuromuscular disease (NMD), genetic testing may help characterize disease and guide care
- Many factors are important to consider when ordering a genetic test, including test type, limitations of testing, logistics and billing, ethical considerations, and patient consent and comprehension.
- Genetic counselors can help navigate testing decisions and communicate with patients about questions and outcomes
- Information in this document highlights key points from an MDA-hosted mini-webinar with a genetic counselor.

[View the companion mini-webinar here.](#)

Inheritance Patterns for NMDs Vary by Disease or Gene¹⁻⁴

Autosomal dominant

A single copy of the mutated gene (from one parent) can cause the disorder

Examples

Myotonic dystrophy,
OPMD, CMT1A

Autosomal recessive

Two copies of the mutated gene (one from each parent) are required to cause the disorder

Examples

SMA, Pompe disease,
sarcoglycanopathies

X-linked inheritance

Characteristics or traits that are influenced by genes on the X chromosome; males more severely affected

Examples

Dystrophinopathies,
CMT1X

Maternal inheritance

Only maternal genetic material passed from parent to offspring

Example

Mitochondrial disease

1. National Human Genome Research Institute. Accessed March 7, 2023. <https://www.genome.gov/genetics-glossary/Autosomal-Dominant-Disorder>. 2. National Human Genome Research Institute. Accessed March 7, 2023. <https://www.genome.gov/genetics-glossary/Autosomal-Recessive-Disorder>. 3. National Human Genome Research Institute. Accessed March 7, 2023. <https://www.genome.gov/genetics-glossary/X-Linked>. 4. Genetic Alliance; District of Columbia Department of Health. Understanding Genetics: A District of Columbia Guide for Patients and Health Professionals. Washington (DC): Genetic Alliance; February 17, 2010. Accessed April 7, 2023. <https://www.ncbi.nlm.nih.gov/books/NBK132149/>

A detailed history and localization of disease can help inform the work-up for genetic testing.

Benefits of Genetic Testing^{1,2}

Why does it matter?



Genetic testing may help identify the genetic aspects of disease, help determine the risk of developing a genetic disorder, and/or achieve a definitive diagnosis



May allow patients to avoid unnecessary or invasive tests, such as muscle or nerve biopsies



Diagnosis with genetic testing can allow for determining appropriate treatment and avoid unnecessary, potentially harmful treatments (e.g., immunosuppressives)



May provide improved access to clinical trials and emerging treatments



Knowledge of disease can aid in family planning, testing at-risk family members, and assessing reproductive risk

National Library of Medicine. MedlinePlus. Genetic Testing. Accessed April 10, 2023. <https://medlineplus.gov/download/genetics/understanding/testing.pdf>. 2. Ng KWP, et al. Front Neurol. 2022;13:997551.

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Types of Genetic Tests¹⁻³

Single-site (targeted) testing¹

Investigate for presence or absence of known familial variant

Single-gene testing²

Analysis of single gene when disease with one known genetic cause highly suspected

Cytogenetic testing³

Focused on detecting chromosomal abnormalities

Next-Generation Sequencing^{1,4}

- Panel testing:
Looks for changes in many genes in a single test
- Whole exome/genome testing:
Analyzes a large bulk of an individual's DNA to locate genetic variations

National Library of Medicine. MedlinePlus. Genetic Testing. Accessed April 10, 2023. <https://medlineplus.gov/download/genetics/understanding/testing.pdf>. 2. Orengo JP, Murdock DR. Genetic testing in neuromuscular disorders. July/August 2019. Accessed March 7, 2023. <https://practicalneurology.com/articles/2019-aug-july/genetic-testing-in-neuromuscular-disorders>. 3. Berisha SZ, et al. *Birth Defects Res.* 2020;112:293-306. 4. Ng KWP, et al. *Front Neurol.* 2022;13:997551.

Multiple factors can help guide selection of the genetic test, including what is known about the patient symptoms, history and family history, and extent of information wanted.

Considerations for Panel Selection



Choose

Accredited lab

- Choose a laboratory with a history of testing in that disease area
 - More likely to be optimized for clinical sensitivity
 - Fewer VUS



Capture

Genes of interest

- Does the panel capture all high-priority genes?
- Consider limitations of NGS panel



Logistics

Logistical considerations



Consider

Is bigger always better?

- Comfort level of the patient with uncertain results
- Often will need parental studies to clarify findings
- Larger panels
- More returned variants



Cost

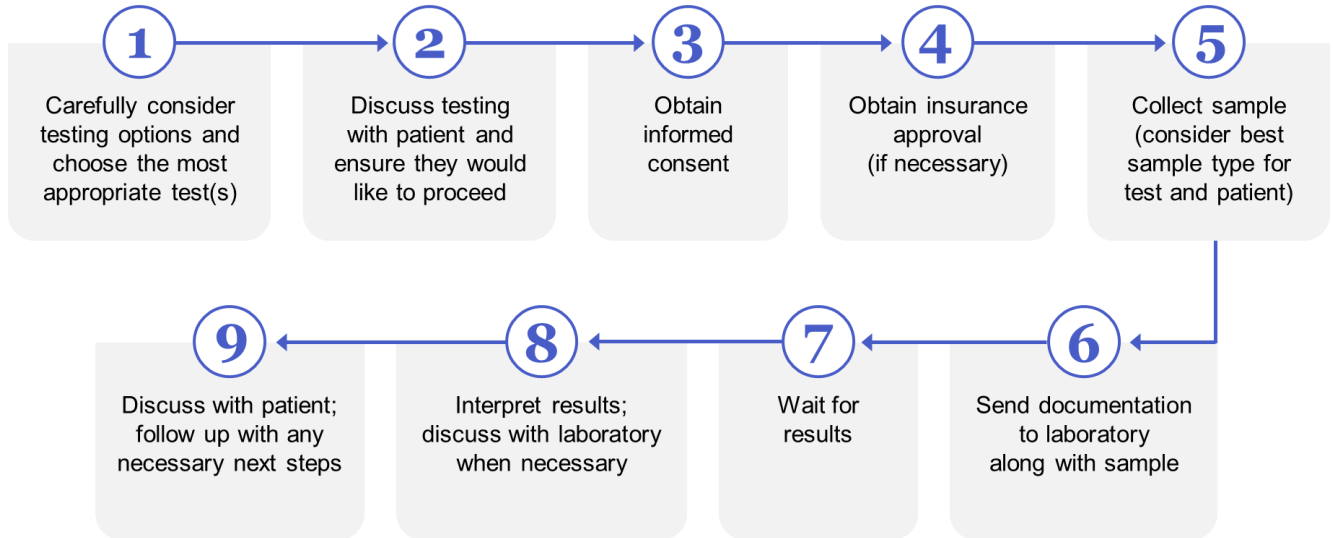
- Check patient's insurance coverage and test turnaround time
- May want to consider sponsored testing options, if available

Ng KWP, et al. *Front Neurol.* 2022;13:997551.

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Example: Ordering a Genetic Test



Examples: When might genetic testing be inappropriate?

Unstable emotional or psychological state of the patient

.....
Example:
Presymptomatic HD testing

Patient unable to properly provide informed consent

.....
Example:
Patient with ID, overt substance abuse, etc.

Improper ordering provider

.....
Testing should be ordered by clinician comfortable interpreting complex genetic testing results

Testing of minors for adult-onset conditions and/or carrier status

Prenatal testing (ongoing pregnancy) for adult-onset disorders

Prohibitive cost of testing

HD, Huntington disease; ID, intellectual disability.

Genetic testing can be complex but can be navigated with the help of a genetic counselor. To find a genetic counselor in your area, consult the [National Society of Genetic Counselors](#)