

From Guidelines to Action: Movement Disorders Care Through Regional & Multidisciplinary Collaboration
Miami, Florida, USA | November 7-8, 2026

International Parkinson and Movement Disorder Society Pan American Section
In collaboration with: Baptist Health

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Update on Genetics and Precision Medicine in the Management of Movement Disorders

Dystonia • Parkinson disease • Ataxia • Chorea • Tremor

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Movement disorders + precision medicine

Definition of precision medicine

General definition – NHGRI / NIH

"An innovative approach that uses information about an individual's genomic, environmental and lifestyle information to guide decisions related to their medical management."

In movement disorders – Parkinson's Foundation

Uses a person's genes, biology, environment and lifestyle to identify treatments that work best for them; biomarkers identify people who share similar traits and may respond to the same treatment.

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core concepts

Clinical principles:

1. phenotype first
2. testing when indicated
3. results interpreted by expert for assessment

Sources: NHGRI/NIH Genetics Glossary (genome.gov); Parkinson's Foundation; MDS; GeneReviews; NCBI; ACMG/AMP

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A precision-medicine framework

1. Confirm phenomenology and distribution.
2. Identify red flags, including childhood onset, progression, developmental features, parkinsonism, myoclonus, episodic symptoms, or family history.
3. Select genetic testing and interpret results in clinical context.
4. Translate the diagnosis into treatment, counseling, surveillance, and trial eligibility.

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Counseling and interpretation pitfalls

- Discuss variable expressivity and reduced penetrance before testing.
- TOR1A has approximately 30% penetrance.
- A pathogenic variant may clarify cause without precisely predicting severity or trajectory.
- Offer appropriate pre-test counseling and involve genetics professionals for uncertain findings and reproductive implications.

Source: GeneReviews, DYT-TOR1A

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A proposed clinic workflow

1. Document phenomenology and a structured family history.
2. Screen for treatable biochemical and genetic mimics.
3. Order a phenotype-matched panel or exome/genome sequencing.
4. Review findings with movement-disorder, genetics, and relevant specialty colleagues; involve the DBS team when indicated.
5. Reanalyze negative genomic testing periodically and use registries for genotype–phenotype context.

A MULTIDISCIPLINARY TEAM

Integrated expertise from neurology, genetics, and relevant specialties to enable accurate diagnosis and personalised care.

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Implementation in the clinic

Before testing

Define the question and consent for possible results.

After testing

Confirm classification, fit the result to the phenotype, and document actions.

For families

Offer cascade testing and explain reduced penetrance.

Build reanalysis into follow-up

Involve genetics for uncertainty or reproductive questions.

Team: movement disorders + genetics + laboratory medicine.

Source: ACMG/AMP; GeneReviews; MDS position statements

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Testing strategy in 2026

Phenotype-led panel

Efficient when the presentation is recognizable; may reduce incidental findings.

Exome or genome sequencing

Consider for complex phenotypes, negative panels, or broad differential diagnoses.

Complementary testing

Add copy number, repeat-expansion, mitochondrial, or biochemical studies when indicated.

Provide phenotype, onset, family structure, imaging, and treatment response; interpret variants with ACMG/AMP criteria.

Source: ACMG/AMP standards; GeneReviews, DYT-TOR1A

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ACMG/AMP 5-tier variant classification

Pathogenic (P)	Disease-causing; used to inform clinical diagnosis and treatment.
Likely Pathogenic (LP)	High probability of being disease-causing (typically >90% certainty).
Uncertain Significance (VUS)	Insufficient or conflicting evidence to determine whether the variant is benign or pathogenic; not used for clinical decision-making.
Likely Benign (LB)	High probability of being harmless.
Benign (B)	Harmless, common, or non-pathogenic variant.

Sources: ACMG/AMP standards

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Reading a genetic report

Actionable result

Ask whether the gene-disease relationship is established, the phenotype fits, and the variant meets ACMG/AMP evidence criteria.

Uncertain

A VUS is not diagnostic. A negative test does not exclude a genetic etiology: consider coverage, structural variants, repeat expansions, mitochondrial disease, and future reanalysis.

Sources: ACMG/AMP standards; GeneReviews; MDSGene

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Other genetic movement disorders

A cross-disorder view

Chorea/dyskinesia	Consider Huntington disease, Wilson disease, and phenocopies.
Tremor/myoclonus	Assess syndromic features, neuropathy, epilepsy, and medications.
Complex parkinsonism/spasticity	Use phenotype-guided panels or exome/genome.
Across disorders	Find treatable mimics, interpret VUS cautiously, and connect results to care.

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Genetics is now clinically relevant in dystonia.

1. Test early-onset, generalized, syndromic, progressive, and familial cases thoughtfully.
2. Seek treatable etiologies, especially dopamine-related and metabolic disorders.
3. Use genomic results to personalize counseling, surveillance, and DBS expectations.
4. Interpret cautiously: uncertainty and reduced penetrance remain, and most gene-specific therapies are investigative.

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Dystonia: Who should undergo genetic testing?

- Childhood- or adolescent-onset dystonia warrants particular consideration.
- Generalized, segmental, multifocal, or progressive presentations raise testing priority.
- Dystonia with developmental, epileptic, cognitive, psychiatric, pyramidal, cerebellar, or parkinsonian features suggests a broader syndrome.
- A compatible family history, atypical isolated dystonia, or early spread can support testing.
- Treatment-responsive features may point to metabolic or neurotransmitter disorders.

Source: contemporary dystonia genetics review, PMC9320296

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Dystonia: High-yield genotype-phenotype patterns

Childhood limb-onset progressive generalized isolated dystonia

TOR1A; recurrent GAG deletion; reduced penetrance

Craniocervical or laryngeal dystonia, often adolescent onset

THAP1; speech and laryngeal involvement can be prominent

Adult-onset cervical dystonia

GNAL or ANO3; often focal or segmental

- Childhood progressive generalized dystonia with developmental features may suggest GCH1, TH, or SPR; KMT2B, VPS16, or EIF2AK2.
- Lower-limb dystonia with diurnal fluctuation suggests GCH1, or SGC2A1.
- Phenotype-genotype overlap is substantial; consider genomic testing when appropriate.

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The don't-miss diagnosis: dopa-responsive dystonia

GCH1-related dopa-responsive dystonia

- Childhood-onset lower-limb dystonia, gait difficulty, parkinsonism, diurnal fluctuation, or sleep benefit are important clues.
- Confirm with a pathogenic or likely pathogenic *GCH1* variant when possible.
- A monitored low-dose levodopa trial is clinically valuable when the condition is suspected.

Recognition can prevent years of disability and unnecessary invasive therapies.

Source: GeneReviews, GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia

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Genetics and botulinum toxin

- Botulinum toxin remains guided by phenotype and muscle pattern, irrespective of genotype.
- Genetic diagnosis can anticipate spread, cranial or bulbar involvement, and coexisting movement features.
- It can inform consideration of systemic therapy or DBS when disease burden evolves.

Genetic yield is generally lower

in focal adult-onset cervical dystonia than in early-onset generalized or complex presentations.

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Genetics and DBS: actionable today

- GPi-DBS is an established option for medically refractory dystonia, though response varies by phenotype and genotype.
- **The strongest evidence for favorable response is in DYT-TOR1A dystonia**
- KMT2B-related dystonia often benefits from GPi-DBS; earlier referral may limit disability and orthopedic complications.
- Outcomes in some **complex dystonias** and rapid-onset dystonia-parkinsonism may be **less predictable**.

Genotype informs counseling;

it should not be the sole determinant of DBS eligibility.

Source: Sarva et al., Journal of the Neurological Sciences, 2024

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Ataxia: testing strategy

Phenotype + tempo

Define episodic, progressive, or congenital ataxia; document eye movements, neuropathy, seizures, and cognition.

Genomic testing

Use repeat-expansion testing when appropriate; exome/genome helps in complex or unsolved cases.

Treatable mimics

Check vitamin E, CoQ10, GLUT1, mitochondrial, immune, and other reversible mimics as indicated.

Ataxia is genetically heterogeneous: pair phenotype, family structure, MRI, and laboratory data with careful variant interpretation.

Sources: MDSGene; GeneReviews; ACMG/AMP

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Parkinson disease + genetics

- Young-onset or atypical parkinsonism warrants testing.
- Red flags: rapid progression, dystonia, ataxia, neuropathy, or strong family history.
- Consider LRRK2, SNCA, PRKN, PINK1, and DJ-1 when the phenotype fits.
- Results can support counseling, family testing, trial eligibility, and care planning.
- A negative panel does not exclude a genetic cause; consider exome/genome and reanalysis.

Testing complements—not replaces—expert clinical diagnosis.

Sources: MDS; GeneReviews; Parkinson disease genetics reviews

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Major advances in Parkinson disease genetics.

- Parkinson's disease is understood as a spectrum involving:
  - monogenic disease (dominant and recessive)
  - moderate-risk variants
  - poligenic susceptibility
  - gene–environment effects
- Key Mendelian genes include SNCA, LRRK2, and VPS35, alongside recessive PRKN, PINK1, and PARK7.
- GBA1 is a major risk gene that connects Parkinson disease with lysosomal and glucocerebrosidase biology.
- Genetic findings can inform diagnosis, counseling, clinical-trial eligibility, and research into biological subtypes.
- Variable penetration and expressivity mean a variant rarely predicts an individual's course with certainty.

PARKINSON DISEASE GENES

DOMINANT
SNCA, LRRK2, VPS35

RECESSIVE
PRKN, PINK1, PARK7

MODERATE RISK VARIANT
GBA1

Source: GeneReviews and contemporary Parkinson genetics reviews.

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LRRK2 and GBA1: precision-medicine targets.

LRRK2

Mutations implicate abnormal kinase signaling as a therapeutic pathway.

LRRK2 inhibitors are being evaluated in genotype-enriched clinical trials.

LRRK2 → Kinase signaling → Cellular effects

GBA1

Variants link Parkinson disease to lyso somal dysfunction and impaired glucocerebrosidase (GCase) biology.

GCase-enhancing and substrate-reduction therapies are under study.

GBA1 → GCase function → Lysosomal function

These targeted approaches remain investigative.

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LRRK2 and GBA1: precision-medicine anchors.

LRRK2

LRRK2 variants implicate kinase signaling; kinase inhibitors are being investigated in genetically stratified trials.

LRRK2 → Kinase signaling

GBA1

GBA1 variants connect Parkinson disease to glucocerebrosidase and lysosomal dysfunction.

GCase-enhancing and substrate-reduction strategies are under study for GBA1-associated disease.

GBA1 → GCase → Lysosomal function

These pathways may inform treatment research beyond carriers, but genotype-specific disease-modifying therapy is not yet routine.

Sources: Parkinson disease genetics reviews; current clinical-trial literature.

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Genetic testing is moving into routine clinical care.

- Consider testing in young-onset Parkinson disease.
- A strong family history can raise the priority for testing.
- Atypical or rapidly progressive parkinsonism may warrant genetic evaluation.
- Consider ancestry and populations with higher prevalence of specific variants.
- Testing may identify people eligible for genetically targeted clinical trials.

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Genetics is moving from diagnosis to trial enablement

- **Testing** can identify candidates for genetically targeted LRRK2 and GBA1 trials.
- **Biomarkers,** including a-synuclein assays, lysosomal measures, and LRRK2 pathway markers, are being studied alongside genotype.
- **Biomarkers** may help define biological subgroups, asses target engagement, and enrich trials.
- **Global programs** such as the Global Parkinson's Genetics Program support discovery, recruitment, and broader ancestry representation.

GENETIC RESULT → PATHWAY OR BIOMARKER SUBGROUP → TRIAL ELIGIBILITY AND TARGET-ENGAGEMENT ASSESSMENT

Source: Global Parkinson's Genetics Program and current Parkinson genetics research.

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Clinical use: test thoughtfully, interpret cautiously.

- Consider testing particularly for young-onset disease, strong family history, atypical features, or interest in targeted trials.
- Results may support counseling, family testing, care planning, and trial screening.
- Polygenic risk scores may explain some differences between carriers but are not validated for routine individual prediction.
- Ancestry-aware research is essential because many discovery datasets have underrepresented populations.

Today, genetics is most useful for diagnosis, counseling, biological research, and trial access— not certain prediction or routine genotype-specific therapy.

Sources: International Parkinson and Movement Disorder Society genetic-testing resources; ancestry-aware genetics research.

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What precision medicine means today

Currently actionable

- Levodopa for dopamine-synthesis disorders
- Ketogenic diet for GLUT1 deficiency
- Carbamazepine for selected paroxysmal dyskinesias
- Genotype-informed DBS counseling
- Molecularly guided surveillance and family counseling.

Not yet routine

- Most monogenic dystonias lack approved gene- or pathway-specific disease-modifying treatment.
- RNA therapies, gene replacement or editing, and pathway-directed approaches remain largely investigative.

Sources: GeneReviews; 2024 review, PubMed 38655812

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Five takeaways for practice

1. **Let phenomenology drive testing.**
2. **Look for treatable mimics.**
3. **Turn results into an action plan.**
4. **A VUS is not diagnostic.**
5. **Reanalyze and decide with the patient.**

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Authoritative resources

GeneReviews (NCBI/NIH)

Monogenic isolated dystonia, TOR1A, and GCH1-related dopa-responsive dystonia.

MDSGene

Curated genotype-phenotype evidence across dystonia and other movement disorders.

ACMG/AMP

Standards for sequence-variant interpretation.

International Parkinson and Movement Disorder Society

Nomenclature, educational resources, and genetic databases.

Selected evidence includes more than **6,000** movement-disorder patients and over **1,000** publications summarized by MDSGene.

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