**Content for Letter of Medical Necessity for**

**Mitochondrial Genome Sequencing**

**Patient Clinical and Family History and Potential Impact of Test Results**

This testing is requested due to this patient’s personal medical history, which includes the following clinical findings:

* Add Relevant Phenotype
* Add Relevant Phenotype
* Add Relevant Phenotype

The patient’s family history is negative for related conditions / unknown / remarkable for the following related clinical features:

The patient has previously had the following uninformative genetic and other testing:

* Add test
* Add test
* Add test

Due to this history, the differential diagnosis includes (list at least 3 conditions you are considering for this patient).

Specifically for my patient, results of mitochondrial genome sequencing will guide prognosis and improve clinical decision-making which can improve clinical outcomes by: (keep all bullets you think are relevant and provide examples/details for each included)

* change in medication: (provide examples of potential new treatments or halting of existing ones that may be recommended based results)
* alteration to diet: (provide examples of potential alteration to diet that may be recommended based results)
* change in planned procedures or surveillance: (provide examples of potential alteration surgery, imaging, and/or diagnostic studies that may be recommended based on results especially state if includes discontinuation of unnecessary procedures)
* Impact on future reproductive planning by informing genetic counseling related to recurrence risk and prenatal diagnosis options: (include and provide additional details if patient’s first degree relative is pregnant or considering pregnancy)

**Background on mitochondrial genome sequencing**

Mitochondrial disorders are clinically variable impacting different organ systems and having significant impact on morbidity and mortality.1 These disorders are difficult to diagnose due to this clinical variability, >350 different causal genes, and limited correlations between genes and clinical features.1 The availability of next-generation sequencing technologies like genome sequencing have shifted diagnostic practice from ‘biopsy-first’ approach requiring a muscle biopsy to direct genetic analysis using more easily accessible samples such as blood.1,2

**Societal guidelines support mitochondrial genome sequencing**

In 2015, a statement from the Mitochondrial Medicine Society recommended analysis of the mitochondrial genome as a first-line test in cases of suspected mitochondrial disease.2 The United Kingdom reiterated this recommendation in 2023 with a practice guideline and added “simultaneous testing of both mtDNA [mitochondrial DNA] and nuclear DNA is recommended if possible.”1

**Identifying the underlying genetic cause impacts patient outcomes**

The comprehensive analysis of sequencing the entire mitochondrial genome has an increased sensitivity compared to targeted analysis.1 A recent study reported a 35% detection rate for simultaneous sequencing in patients with suspected mitochondrial disorders.3 For patients with a confirmed mitochondrial genetic cause, gene and variant specific treatment recommendations include tailored medication treatment, avoidance of specific medication, avoidance of certain environmental triggers, vitamin supplementation, and increased monitoring due to high risk of organ specific complications.4,5

**References**

1. Mavraki, E., et al., *Genetic testing for mitochondrial disease: the United Kingdom best practice guidelines.* Eur J Hum Genet, 2023. **31**(2): p. 148-163.

2. Parikh, S., et al., *Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society.* Genet Med, 2015. **17**(9): p. 689-701.

3. Wu, T.H., et al., *Use of dual genomic sequencing to screen mitochondrial diseases in pediatrics: a retrospective analysis.* Sci Rep, 2023. **13**(1): p. 4193.

4. Parikh, S., et al., *Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society.* Genet Med, 2017. **19**(12).

5. Tinker, R.J., et al., *Current and Emerging Clinical Treatment in Mitochondrial Disease.* Mol Diagn Ther, 2021. **25**(2): p. 181-206.