Mitochondrial Disease Version 2.0 NINDS CDE Project
Genetics Subgroup Summary

Definition of Primary Mitochondrial Disease (Genetically Determined Mitochondrial Disorders)

Primary mitochondrial diseases are genetic disorders that can be caused by either pathogenic genetic changes in the mitochondrial DNA (mtDNA) or changes in the nuclear DNA that lead to dysfunction of the mitochondria and inadequate production of energy. Those caused by genetic changes in mtDNA in the form of point variant or single deletion/duplication, are transmitted by maternal inheritance or acquired de novo. Nuclear DNA changes can present in an autosomal dominant, autosomal recessive, or X-linked pattern of inheritance, or be acquired de novo or through germ line mosaicism. Nuclear DNA changes may also cause mtDNA alteration (point variant, deletion and/or depletion).

Role of the NINDS Mitochondrial Disease v2.0 Common Data Element (CDE) Genetics Subgroup

The role of the subgroup was to clarify the methodology needed to properly identify these genetic variants causing primary mitochondrial disorders and define the criteria needed to establish pathogenicity. Nuclear DNA and mtDNA sequencing data will be determined by a variety of methods.

The pathogenic genetic changes considered by this subgroup are:

1. Nuclear DNA variants in genes necessary for normal mitochondrial function
2. mtDNA point variants
3. mtDNA deletions and duplications
4. mtDNA depletion
5. The degree of heteroplasmy for point variants and deletions in the affected tissue

In the case of multiple mtDNA deletions, the totality of the deletions should be considered in relation to heteroplasmy. The subgroup considered the source of tissue to determine these genetic changes (blood, muscle, etc.), and the technology used, such as single gene sequencing, panel gene sequencing, whole exome sequencing (WES), and whole genome sequencing (WGS). The method for determining these changes could be Sanger sequencing, Illumina based next generation sequencing (NGS), Illumina duplex sequencing, or Nanopore sequencing. Variants must be validated by comparison to a control sample. Furthermore, special bioinformatic pipelines were assessed for highly sensitive detection of deletions or point variants.

The following databases* list known DNA variants that are associated with mitochondrial diseases:
MITOMAP (https://www.mitomap.org/MITOMAP)
gnomAD (https://gnomad.broadinstitute.org)
dbSNP (https://www.ncbi.nlm.nih.gov/snp/)
ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/)
ClinGen (https://clinicalgenome.org/)
MSeqDR (https://mseqdr.org/MITO/genes)
POLG database (https://tools.niehs.nih.gov/polg/)
*These databases are constantly being updated, please make sure you use the most up to date information

Summary of Recommendations

Subdomain	CRF Name	Classification
Laboratory Tests and Biospecimens/Biomarkers	Primary Mitochondrial Disease (PMD) Genetics	Core; Supplemental – Highly Recommended; Supplemental