**Part 1 – Clinical Description**

1. **\***Primary Clinical Diagnosis of Mitochondrial Disease (Choose one):1

|  |  |
| --- | --- |
| 1: Alpers syndrome: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 2: Cardiomyopathy: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 3: Chronic progressive external ophthalmoplegia (CPEO): | [ ] Present [ ] Absent \*Age at symptom onset: |
| 4: Chronic progressive external ophthalmoplegia (CPEO "plus"): | [ ] Present [ ] Absent \*Age at symptom onset: |
| 5: Maternally Inherited Diabetes and Deafness (MIDD): | [ ] Present [ ] Absent \*Age at symptom onset: |
| 6: Kearns-Sayre syndrome (KSS): | [ ] Present [ ] Absent \*Age at symptom onset: |
| 7: Leber hereditary optic neuropathy (LHON): | [ ] Present [ ] Absent \*Age at symptom onset: |
| 8: Leigh syndrome: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 9: Maternal-inherited deafness: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 10: MELAS: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 11: MNGIE: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 12: Multi-systemic syndrome: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 13: MERRF: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 14: Myopathy: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 15: Neuropathy, ataxia and retinitis pigmentosa (NARP): | [ ] Present [ ] Absent \*Age at symptom onset: |
| 16: Pearson syndrome: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 17: Reversible infantile myopathy with cytochrome c oxidase deficiency:  | [ ] Present [ ] Absent \*Age at symptom onset: |
| 18: Ataxia Neuropathy syndrome: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 19: Other POLG related disorders: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 20. Aminoglycoside-induced deafness: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 21: Barth syndrome: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 22: Encephalomyopathy: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 23: Hepatocerebral syndrome: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 24: Leukoencephalopathy: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 25: Encephalopathy: | [ ] Present [ ] Absent \*Age at symptom onset: |
| 26: Other clinical syndrome/symptom, specify: | [ ] Present [ ] Absent \*Age at symptom onset: |

1. Signs Supportive of PMD Diagnosis:

|  |  |
| --- | --- |
| Bilateral basal ganglia lesions: | [ ] Present [ ] Absent [ ] N/A  |
| Lactate peak on MRI: | [ ] Present [ ] Absent [ ] N/A  |
| Metabolic stroke: | [ ] Present [ ] Absent [ ] N/A  |
| Elevated tissue lactate: | [ ] Present [ ] Absent [ ] N/A  |
| Elevated blood alanine: | [ ] Present [ ] Absent [ ] N/A  |
| Elevated CPK: | [ ] Present [ ] Absent [ ] N/A  |
| Elevated GDF-15: | [ ] Present [ ] Absent [ ] N/A  |
| Elevated tissue ragged-red fibers: | [ ] Present [ ] Absent [ ] N/A  |
| Tissue COX deficient stain: | [ ] Present [ ] Absent [ ] N/A  |
| Tissue SDH positive stain: | [ ] Present [ ] Absent [ ] N/A  |
| Abnormal mitochondria in electron microscope: | [ ] Present [ ] Absent [ ] N/A  |
| Abnormal OXPHOS function: | [ ] Present [ ] Absent [ ] N/A  |
| Other, specify: | [ ] Present [ ] Absent [ ] N/A  |

**Part II – Genetics Summary**

1. Was genetic testing performed? [ ]  Yes [ ]  No

If YES, please answer questions below:

* 1. What year was the genetic testing performed?
	2. Indicate the source(s) of the genetic test results: (Choose all that apply)

[ ]  Geneticist

[ ]  Genetic counselor

[ ]  Neurologist

[ ]  Medical records

[ ]  Other general practitioner

[ ]  Other specialty physician

[ ]  Other, specify:

* 1. Was the participant informed of the test results? [ ]  Yes [ ]  No
		1. If YES, who informed them of the results?

[ ]  Geneticist

[ ]  Genetic Counselor

[ ]  Metabolic specialist

[ ]  Neurologist

[ ]  Self (results from Direct-to-Consumer test)

[ ]  Other, specify:

* 1. Known Variant/s in participant’s DNA:1 [ ]  Present [ ]  Absent [ ]  Unknown
		1. If present or absent, describe:1
1. Has the participant had a sample drawn for DNA banking? [ ]  Yes [ ]  No [ ]  Unknown

If YES,

* 1. Specify the type of sample drawn:

[ ]  Blood draw

[ ]  Buccal smear (cheek swab)

[ ]  Saliva

[ ]  Urine sediment

[ ]  Muscle tissue

[ ]  Other, specify:

* 1. Specify the study for which the sample was initially taken:
	2. Specify where the sample is banked, if known:
	3. Did the participant sign a consent form at the time the sample was taken?

[ ]  Yes [ ]  No [ ]  Unknown

* 1. Does the consent form for this sample allow for sharing of the sample? [ ]  Yes [ ]  No
	2. Has the participant given a sample of blood to a repository? [ ]  Yes [ ]  No

If YES,

* + 1. Name of repository:
		2. Sample ID:
		3. Repository contact:
		4. Type of tissue collected:
		5. GUID:
1. Has the participant registered for organ donation? **[ ]** Yes **[ ]** No
	1. If YES, name of repository:
2. Is a sample available from a family member? **[ ]** Yes **[ ]** No

If YES,

* 1. Name of repository:
	2. Sample ID:
	3. Repository contact:
	4. Type of tissue collected:
	5. GUID:

**Part III – Study Description**

1. Study type(s) (Choose all that apply):2

[ ]  Longitudinal

[ ]  Case-control

[ ]  Case set

[ ]  Control set

[ ]  Parent-offspring trios

[ ]  Cohort

[ ]  Clinical trial

[ ]  Other, specify:

1. Is aggregate-level data appropriate for General Research Use? 2 [ ] Y [ ]  N
2. Please check all data types expected for this study: 2
	1. General

[ ]  Individual Phenotype

[ ]  Individual Genotype

[ ]  Individual Sequencing

[ ]  Supporting Documents

[ ]  Transcriptomic

[ ]  Proteomic/Metabolomic

[ ]  RNA seq

[ ]  Images

* 1. Sample Types

[ ]  Germline

[ ]  Tumor/Normal

[ ]  DNA

[ ]  RNA

[ ]  Mitochondria

[ ]  Microbiome

[ ]  From Repository

[ ]  Other tissue, specify:

* 1. Array Data

[ ]  SNP Array

[ ]  Expression Array

[ ]  Methylation Array

* 1. Genotypes

[ ]  Array derived genotypes

[ ]  CNV calls from microarray

[ ]  CNV calls derived from Sequencing

[ ]  Genotype calls derived from Sequence

[ ]  Somatic SNV (MAF)

[ ]  Array CGH CNVs

* 1. Sequencing

[ ]  Whole Genome

[ ]  Whole Exome

[ ]  Targeted Genome

[ ]  Targeted Exome

[ ]  Whole Transcriptome

[ ]  Targeted Transcriptome

[ ]  Epigenomic Marks

[ ]  Sanger

[ ]  16S rRNA

* 1. Analysis

[ ]  Association/Linkage results

[ ]  Array-derived expression

[ ]  Bulk RNA Seq derived expression

[ ]  Array-derived methylation

**Part IV – Genotype Platform Information**

1. Name and version: 2
2. Vendor: 2
3. # Probes: 2
4. URL: 2
5. Description (optional): 2

**Part V – Variant/Mutation Analysis**

1. \*\*Lab name:
2. \*\*Date report issued:
3. \*\*Variant analysis results available on this participant: [ ]  Yes [ ]  No

 (IF NO, Stop completing form)

1. \*\*Variant analysis performed on the participant: [ ]  Yes [ ]  No
2. If NO, was variant analysis performed on a family member? [ ]  Yes [ ]  No
3. If NO, provide explanation:
4. \*\*Variant analysis results:
5. Variant(s) detected:

[ ]  Homozygous

[ ]  Compound Heterozygous

[ ]  Heterozygous

[ ]  Hemizygous

[ ]  Digenic (variants in more than one gene)

[ ]  No pathogenic variant detected

1. Are there additional variants in other genes of unknown significance? [ ]  Yes [ ]  No

If YES, indicate:

1. Are there additional genes sequenced with no variants detected? [ ]  Yes [ ]  No

If YES, indicate:

1. \*\*What type of testing was performed?
	1. [ ]  mtDNA panel testing
		1. What tissue?

[ ]  Blood

[ ]  Saliva

[ ]  Buccal smear

[ ]  Urine sediment

[ ]  Muscle

[ ]  Liver

[ ]  Other, please specify:

* + 1. What genes?
	1. [ ]  mtDNA genome deletion/duplication analysis
		1. What tissue?

[ ]  Blood

[ ]  Saliva

[ ]  Buccal smear

[ ]  Urine sediment

[ ]  Muscle

[ ]  Liver

[ ]  Other, please specify:

* + 1. What genes?
	1. [ ]  Karyotype
		1. What tissue?

[ ]  Blood

[ ]  Amnio

[ ]  Skin

[ ]  Other, please specify:

1. \*\*Allele specific information
2. Allele #1
3. Gene Name:
4. Variant Class:

[ ]  Reduced Number of Copies

[ ]  Increased Number of Copies

[ ]  Missense

[ ]  Nonsense

[ ]  Splice

[ ]  Pseudoexon

[ ]  Potential (variant of unknown significance)

[ ]  Subexonic Insertion/Deletion

[ ]  Other, specify:

1. \*\*For Exonic Deletions/ Duplications:
	* 1. Was the copy number directly tested for all exons? [ ]  Yes [ ]  No [ ]  Unknown
		2. Are the limits of the copy number completely defined? [ ]  Yes [ ]  No [ ]  Unknown
			1. First Exon affected:
			2. Last Exon affected:
			3. Whole gene affected? [ ]  Yes [ ]  No [ ]  Unknown
			4. Predicted reading frame: [ ]  In [ ]  Out [ ]  Unknown
			5. Are known gene promoters affected: [ ]  Yes [ ]  No [ ] Unknown
2. \*\*For Missense/nonsense variant or Pseudoexons:
	* 1. Was the entire coding region sequenced: [ ]  Yes [ ]  No
		2. Targeted variant analysis only: [ ]  Yes [ ]  No
			1. If YES, type of analysis: [ ]  Hot-spot [ ]  Known familial variant [ ]  Other, specify:
		3. Missense/nonsense variant location (Choose one)
			1. Exon (Point Variant):
			2. Intron:
			3. Other, specify:
		4. Missense/nonsense variant subclass information:
			1. Insertion Deletion: [ ]  Insertion [ ]  Deletion [ ]  Insertion/Deletion
			2. Nonsense Type: [ ]  UAA [ ]  UAG [ ]  UGA [ ]  Not applicable
3. \*\*mRNA analysis
	* 1. mRNA analysis performed: [ ]  Yes [ ]  No [ ]  Unknown
			1. If YES, were implications confirmed: [ ]  Yes [ ]  No
4. \*\*Variant Information (HGVS Nomenclature)
	* 1. cDNA: (if relevant, data to be entered by site)
		2. mRNA: (if relevant, data to be entered by site)
		3. Protein: (if relevant, data to be entered by site)
5. \*\*Allele Specific Information
6. Allele #2
7. Was a second disease allele identified? [ ]  Yes [ ]  No (Skip to question 24)
8. Is allele #2 identical to allele #1 (Homozygous only): [ ]  Yes (Skip to question 24) [ ]  No

If NO, repeat filling out allele specific information for Allele #2.

1. \*\*For Mitochondrial DNA variant:
	1. Quantitative analyses (Heteroplasmy assessment)

[ ]  Evaluation method

[ ]  Restriction PCR

[ ]  Deep sequencing

[ ]  Allele specific PCR

[ ]  qPCR (deletions, depletion)

[ ]  Southern blot

[ ]  Other, specify:

[ ]  Heteroplasmy level

[ ]  Blood

[ ]  Muscle

[ ]  Urinary sediment

[ ]  Buccal cells

[ ]  Saliva

[ ]  Other, specify:

1. Please fill out the tables and associated questions. One row in the table should be filled out for each individual variant.
	1. \*Table 1: Genetic Testing Results for nuclear DNA

| Gene\*\* | DNA change[[1]](#footnote-1) | Tissue\*\* | Test Methodology\*\* | Region Tested: Coverage\*\* | Clinical Category\*\* | References |
| --- | --- | --- | --- | --- | --- | --- |
| Data to be filled in by site | Data to be filled in by site | [ ]  Blood[ ]  Amniocytes[ ]  Skin [ ]  Other, specify: | Data to be filled in by site | Data to be filled in by site | [ ]  Definite pathogenic[ ]  Likely pathogenic[ ]  Variant of uncertain significance[ ]  Likely benign[ ]  Definitely benign | Data to be filled in by site |

* 1. \*Table 2: Genetic Testing Results for mtDNA

| Gene\*\* | DNA changei | Tissue\*\* | Heteroplasmy Levels\*\* | Test Methodology\*\* | Region Tested: Coverage\*\* | Clinical Category\*\* | References |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Data to be filled in by site | Data to be filled in by site | [ ]  Blood[ ]  Urine[ ]  Muscle[ ]  Buccal[ ]  Other, specify: | Data to be filled in by site | Data to be filled in by site | Data to be filled in by site | [ ]  Definite pathogenic[ ]  Likely pathogenic[ ]  Variant of uncertain significance[ ]  Likely benign[ ]  Definitely benign | Data to be filled in by site |

1. \*\*Basis for the evaluation of the clinical category:

[ ]  Previously reported

[ ]  Familial segregation

[ ]  Prevision software (name of the software)

[ ]  Experimental validation

[ ]  Functional complementation in cultured cells

[ ]  Other, specify:

1. For Mitochondrial DNA variant:
2. \*\*Basis for the clinical evaluation of the clinical category:

[ ]  Previously reported

[ ]  Familial segregation

[ ]  Tissular segregation

[ ]  Prevision software (name of the software)

[ ]  \*\*Experimental validation

[ ]  Transfer into cybrid cells

[ ]  Single muscle fiber

Recorder Signature: Date:

## General Instructions

This form contains data elements collecting information on the genetic etiology of participants with primary mitochondrial disease (PMD). The focus is on variables related to sample processing and genetic testing results while also capturing some information on variables related to phenotype in both the clinical and research setting.

Important note: Some of the data elements included on this CRF Module are classified as Core (i.e., strongly recommended for all mitochondrial disease clinical studies to collect) or Supplemental – Highly Recommended (i.e., essential information for specified conditions, study types, or designs), as indicated by asterisks below, and should be collected if genetics studies are performed.

\*Element is classified as Core

\*\*Element is classified as Supplemental – Highly Recommended

The remaining data elements are Supplemental (i.e., non-Core) and should only be collected if the research team considers them appropriate for their study.

Please see the Data Dictionary for element classifications.

## Specific Instructions

Please see the Data Dictionary for definitions for each of the data elements included in this CRF Module.

* Date – Date/time should be recorded to the level of granularity known (e.g., year, year and month, complete date plus hours and minutes, etc.) and in an unambiguous format acceptable to the study database like DD-MMM-YYYY. When date/time data are prepared for aggregation or sharing, they should be converted to the format specified by [ISO 8601](https://www.iso.org/iso-8601-date-and-time-format.html); YYYY-MM-DD T:hh:mm:ss.

References

1Question and permissible values from [Coriell Institute for Medical Research](https://www.coriell.org/1/About-Us/Legal-Notice) used and modified with permission.

2Question and permissible values from dbGaP/database of Genotypes and Phenotypes/ National Center for Biotechnology Information, National Library of Medicine (NCBI/NLM) <https://www.ncbi.nlm.nih.gov/gap> used and modified with permission.

1. i Note: The mtDNA genome is rather small, completely sequenced and numbered. According to current recommendations variants in the mitochondrial DNA should be described in relation to the full mitochondrial DNA sequence, i.e., for human the Homo sapiens mitochondrion, complete genome(GenBank [NC\_012920.1](http://www.ncbi.nlm.nih.gov/nuccore/NC_012920)). Descriptions should be preceded by "m.", like m.8993T>C ([*see Recommendations*](http://www.hgvs.org/mutnomen/recs.html#prefix)). The mtDNA encodes a range of different proteins. To prevent confusion, changes at protein level should be described including a reference to the protein changed, like ATP6:p.Leu156Pro (GenBank [YP\_003024031.1](http://www.ncbi.nlm.nih.gov/protein/251831112), ATP synthase 6). (*HGVS recommendations)* [↑](#footnote-ref-1)