## Biomarker Testing

1. Was a biomarker analysis done?

[ ]  Yes

[ ]  No

If YES, please answer questions below:

1. Source:

[ ]  Blood (serum/plasma)

[ ]  Buccal swab

[ ]  CSF

[ ]  Fibroblasts

[ ]  Imaging

[ ]  MRS

Location:

[ ]  Brain

[ ]  Liver

[ ]  Muscle

[ ]  Other, specify:

[ ]  Ultrasound

Location:

[ ]  Brain

[ ]  Liver

[ ]  Muscle

[ ]  Other, specify:

[ ]  Other, specify:

Location:

[ ]  Brain

[ ]  Liver

[ ]  Muscle

[ ]  Other, specify:

[ ]  Induced pluripotent stem cells (iPS)

[ ]  Kidney biopsy

[ ]  Leukocytes

[ ]  Liver biopsy

[ ]  Lymphoblasts (EBV)

[ ]  Lymphocytes

[ ]  Muscle biopsy

[ ]  Organoid(s):

[ ]  Brain

[ ]  Kidney

[ ]  Liver

[ ]  Other, specify:

[ ]  Red blood cells

[ ]  Whole Blood

[ ]  Cultured Cells

[ ]  Saliva

[ ]  Urine

[ ]  Other, specify:

1. Clinical assessments:

[ ]  Cardiac evaluation:

[ ]  Echocardiogram

[ ]  EKG

 [ ]  Holter Monitor

[ ]  MRI

[ ]  Other, specify:

[ ]  Ergometry

[ ]  Head circumference

[ ]  Hearing

[ ]  Height

[ ]  Indirect calorimetry

[ ]  Vision

[ ]  Weight

[ ]  Other, specify:

1. Which biomarker(s) were assessed from the specimen's (serum/plasma) sample?

[ ]  Acylcarnitines

[ ]  Amino acids

[ ]  Ammonia

[ ]  Carnitine levels

[ ]  CBC

[ ]  Cell-free mitochondrial DNA (cf-mtDNA)

[ ]  CPK

[ ]  Creatine

[ ]  Cystatin C

[ ]  Electrolytes

[ ]  Endocrine testing:

[ ]  A1C

[ ]  Cortisol

[ ]  Free fatty acids

[ ]  Glucose

[ ]  Insulin

[ ]  Ketone bodies

[ ]  Thyroid

[ ]  Other, specify:

[ ]  Fibroblast growth factor 21 (FGF21)

[ ]  Growth differentiation factor 15 (GDF15)

[ ]  Hepatic panel:

[ ]  Albumin

[ ]  Alk Phos

[ ]  ALT

[ ]  AST

[ ]  GGT

[ ]  INR

[ ]  PT

[ ]  PTT

[ ]  Other, specify:

[ ]  Lactate

[ ]  Lactate/pyruvate ratio

[ ]  LDH

[ ]  Lipid panel

[ ]  Metabolomics:

[ ]  Targeted

[ ]  Untargeted

[ ]  Vitamin levels:

[ ]  B12

[ ]  Folate

[ ]  Niacin

[ ]  Pyridoxine

[ ]  Riboflavin

[ ]  Thiamine

[ ]  Other, specify:

[ ]  Pyruvate

[ ]  Purines and pyrimidines

[ ]  Other, specify:

1. Which biomarker(s) were assessed from the urine sample?

[ ]  Acylglycines

[ ]  Amino acids

[ ]  Metabolomics:

[ ]  Targeted

[ ]  Untargeted

[ ]  mtDNA heteroplasmy

[ ]  Organic acids

[ ]  Purines and pyrimidines

[ ]  Urinalysis (UA)

[ ]  Other, specify:

1. Which biomarker(s) were assessed from the cerebrospinal fluid (CSF) sample?

[ ]  5-methyltetrahydrofolate

[ ]  Amino acids

[ ]  Cell count

[ ]  GABA

[ ]  Glucose (with simultaneous blood glucose)

[ ]  Lactate

[ ]  Metabolomics:

[ ]  Targeted

[ ]  Untargeted

[ ]  Neurotransmitters

[ ]  Protein

[ ]  Pyruvate

[ ]  Other, specify:

1. Which biomarker(s) were assessed from the specimen's fibroblasts sample?

[ ]  ATP synthesis

[ ]  Blue native gel electrophoresis (OXPHOS)

[ ]  Coenzyme Q10

[ ]  High resolution respirometry

[ ]  Lactate/pyruvate ratio

[ ]  OXPHOS enzymology

[ ]  Pyruvate dehydrogenase enzymology

[ ]  Seahorse live cell metabolic analysis

[ ]  Other, specify:

1. Which biomarker(s) were assessed from the specimen's leukocytes sample?

[ ]  Coenzyme Q10

[ ]  Intracellular free glutathione (fGSH), oxidized disulfide (GSSG), fGSH/GSSG ratio

[ ]  mtDNA copy number

[ ]  mtDNA deletion/duplication

[ ]  Pyruvate dehydrogenase enzymology

[ ]  Thymidine phosphorylase enzymology

[ ]  Other, specify:

1. Which biomarker(s) were assessed the specimen's lymphoblast sample?

[ ]  ATP synthesis

[ ]  High resolution respirometry

[ ]  Seahorse live cell metabolic analysis

[ ]  Other, specify:

1. Which biomarker(s) were assessed from the specimen's muscle biochemistry?

[ ]  ATP synthesis

[ ]  Blue native gel electrophoresis

[ ]  Coenzyme Q10

[ ]  Glutathione content

[ ]  High resolution respirometry

[ ]  mtDNA copy number

[ ]  mtDNA deletion/duplication

[ ]  OXPHOS enzymology

[ ]  Pyruvate dehydrogenase enzymology

[ ]  Seahorse live cell metabolic analysis

[ ]  Other, specify:

1. Which biomarker(s) were assessed from the specimen's muscle histology?

[ ]  Combined SDH + COX

[ ]  Cytochrome C Oxidase (COX) (Complex IV)

[ ]  Gomori trichrome

[ ]  Nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR)

[ ]  Succinate dehydrogenase (SDH)

[ ]  Other, specify:

1. Which biomarker(s) were assessed from the specimen's genetics?

| **Biomarker** | **Specimen Type** |
| --- | --- |
| [ ]  Exome sequencing (NGS) (nDNA) | [ ]  Buccal swab[ ]  Cultured cells[ ]  Leukocytes[ ]  Muscle[ ]  Urine[ ]  Whole blood[ ]  Other, specify: |
| [ ]  Whole genome sequencing | [ ]  Buccal swab[ ]  Cultured cells[ ]  Leukocytes[ ]  Muscle[ ]  Urine[ ]  Whole blood[ ]  Other, specify: |
| [ ]  Gene sequencing panel  | [ ]  Buccal swab[ ]  Cultured cells[ ]  Leukocytes[ ]  Muscle[ ]  Urine[ ]  Whole blood[ ]  Other, specify: |
| [ ]  RNA analysis | [ ]  Buccal swab[ ]  Cultured cells[ ]  Leukocytes[ ]  Muscle[ ]  Urine[ ]  Whole blood[ ]  Other, specify: |
| [ ]  Mitochondrial gene expression profiling | [ ]  Buccal swab[ ]  Cultured cells[ ]  Leukocytes[ ]  Muscle[ ]  Urine[ ]  Whole blood[ ]  Other, specify: |
| [ ]  Mitochondrial haplotype | [ ]  Buccal swab[ ]  Cultured cells[ ]  Leukocytes[ ]  Muscle[ ]  Urine[ ]  Whole blood[ ]  Other, specify: |
| [ ]  mtDNA copy number | [ ]  Leukocytes[ ]  Liver[ ]  Muscle[ ]  Other, specify: |
| [ ]  mtDNA deletion/duplication | [ ]  Leukocytes[ ]  Liver[ ]  Muscle[ ]  Other, specify: |
| [ ]  mtDNA sequencing | [ ]  Buccal swab[ ]  Cultured cells[ ]  Leukocytes[ ]  Muscle[ ]  Urine[ ]  Whole blood[ ]  Other, specify: |
| [ ]  Other, specify: | [ ]  Buccal swab[ ]  Cultured cells[ ]  Leukocytes[ ]  Muscle[ ]  Urine[ ]  Whole blood[ ]  Other, specify: |

1. Specify other biomarker(s) assessed from specimen sources not listed above:

Recorder Signature: Date:

## General Instructions

This case report form contains data elements that assess biomarkers with potential utility to confirm or evaluate mitochondrial disease. Data collected may be used to substantiate or provide additional evidence of a mitochondrial disease diagnosis, indicate severity of disease, determine standard of care, and/or monitor medication/therapy.

Important note: None 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). All data elements are classified as Supplemental 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.

* For each biomarker, the source should be specified. If not listed, use “other” and designate source.
* Source type – Kidney and liver biopsy samples may be taken from organs in vivo or from whole organs ex vivo.
* Vitamin level type – For assessment of vitamin B12 or folate deficiency, evaluation of plasma methylmalonic acid (MMA) and total homocysteine is recommended.
* 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

Please see Guidance Document.