Overview
Mitochondrial Disease Working Group: Exercise Physiology

The National Institute of Neurological Disorders and Stroke (NINDS) Mitochondrial Disease (Mito) Exercise Physiology Common Data Elements (CDEs) Working Group (WG) compiled a list of instrument recommendations through thorough review and discussion of current instruments and measurements in use as well as through analysis of relevant literature.

The tested variables for this WG included the following categories along with rationale:

Exercise Intolerance

Exercise intolerance is a common and leading complaint for patients with mitochondrial disease and manifests clinically as dyspnea, tachycardia, and early muscle fatigue during low levels of exertion. During exercise, an inability to increase muscle oxygen extraction and an excessive cardiopulmonary response have been measured and believed to contribute to these symptoms of exercise intolerance in patients with mitochondrial disease (Taivassalo et al 2003).

Poor exercise tolerance in mitochondrial patients often leads to physical inactivity; the deleterious effects of which become superimposed upon a patient's already impaired mitochondrial function, thus contributing to worsening of the exercise intolerance in these patients.

Endurance

Numerous studies of animal models (Wenz et al., 2009; Safdar et al., 2011) and human patients with varying mitochondrial myopathies (both nuclear and mitochondrial DNA encoded) demonstrate the benefits of endurance exercise training in mitochondrial disease. These studies in mitochondrial patients have shown: increased mitochondrial content and enzyme activity; increased antioxidant enzyme activity and lower markers of oxidative stress; increased maximal oxygen uptake; increased exercise performance; increased walking distance; increased ADP recovery rates; and increased peripheral muscle strength with decreased minute ventilation. Other findings include improved clinical symptoms and a decrease in resting and post-exercise blood lactate levels (Cejudo et al., 2005; Jeppesen et al., 2006; Jeppesen et al., 2009; Lima et al., 2013; Siciliano etal., 2012; Taivassalo et al., 1998; Taivassalo et al., 2001; Taivassalo et al., 2006). If training is maintained, these findings are sustained over time.

Endurance exercise training has also been found to improve quality of life using scales such as the SF-36 (Cejudo et al., 2005; Siciliano et al., 2012; Taivassalo et al., 1998; Taivassalo et al., 2006).

Resistance

Satellite cells are dormant myoblasts that can be stimulated to re-enter the cell cycle and fuse with existing myofibers in response to signals for muscle growth associated with resistance training and thus contribute (McKinnell et al., 2005; Taivassalo et al., 1999) wild-type mtDNA and shift the mtDNA heteroplasmy to a higher wild-type:mutant ratio. Following resistance training, even in the absence of muscle hypertrophy, differentiating satellite cells can also increase in size and number (Joanisse et al., 2013) and this may have additional benefits in terms of mitochondrial DNA shifting.

Resistance training in patients with mtDNA alterations has been shown to (i) increase muscle strength; (ii) increase myofiber regeneration; (iii) increase satellite cell recruitment; and (iv) improve muscle oxidative capacity. Murphy et al., 2008).

Resistance, Endurance, or Both?

Several studies have demonstrated a direct relationship between the proportion of skeletal muscle mutant mtDNA and the degree of exercise intolerance in mitochondrial myopathy patients (Jeppesen et al., 2003; Taivassalo et al. 2003), suggesting that strategies to reduce the mtDNA mutant load could improve exercise tolerance.

Deconditioning

Compliance with exercise programs can be difficult in any patient but compliance may be further reduced in mitochondrial patients secondary to the exercise intolerance that predominates. Cessation of training (detraining) results in return of physiological adaptations to baseline (Jeppesen et al., 2006; Taivassalo et al., 2006)

Safety

Sporadic reports have been published demonstrating theoretical concern for the safety of exercise in mitochondrial patients (Adhihetty et al., 2007; Czell et al., 2012). Studies have demonstrated that plasma lactate levels elevate quicker in patients with mitochondrial myopathy during exercise than in controls (Lindholm et al., 2004); however, endurance exercise training is associated with a lowering of exercise plasma lactate levels at the same absolute exercise intensity (Jeppesen et al., 2013; Phillips et al., 1995). Several studies have shown that endurance exercise results in lower plasma lactate accumulation in patients with mitochondrial disease (Siciliano et al., 2012; Taivassalo et al.,1998; Taivassalo et al., 2006).

The vast majority of studies report no deleterious effects in patients with mitochondrial myopathy from exercise training, either resistance or endurance. In particular there are no reports of elevated creatine kinase levels and no reports of increased musculoskeletal injuries in mitochondrial patients during supervised progressive exercise aimed at physiological adaptation (Bates et al., 2013; Jeppesen et al., 2006; Jeppesen et al., 2009; Taivassalo et al., 2001; Taivassalo et al., 2006). The impact of exercise training on heteroplasmic shifting and ability to increase wild-type mtDNA needs further investigation.

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Summary Recommendations

READ ME: This is a recommendations summary document of the instruments/measures/case report forms, sorted by domain and subdomain. Details of the recommendations follow this spreadsheet in the form of information documents (e.g., Notices of Copyright) or case report forms and CDE details.

Instrument / Scale Name*Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs*	Classification *[e.g., Core, Supplemental (also those highly-recommended), or Exploratory]*	Domain	Sub-domain
2 Minute Walk Test	Exploratory	Outcomes and Endpoints	Functional Status
6 Minute Walk Test	Supplemental	Outcomes and Endpoints	Functional Status
Gross Motor Function Measure (GMFM)	Supplemental	Outcomes and Endpoints	Functional Status
Physical Activity Questionnaire for Adolescents	Supplemental	Outcomes and Endpoints	Functional Status
The Borg Scale of Perceived Exertion	Supplemental– Highly Recommended for exercise physiology studies	Outcomes and Endpoints	Functional Status
Manual Muscle Testing-Using the Medical Research Council Grading Scale	Supplemental	Outcomes and Endpoints	Muscle Strength Testing
Maximum Voluntary Isometric Contraction Testing (MVICT)	Supplemental	Outcomes and Endpoints	Muscle Strength Testing
Alberta Infant Motor Scale	Exploratory	Outcomes and Endpoints	Pediatric

Instrument / Scale Name*Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs*	Classification *[e.g., Core, Supplemental (also those highly-recommended), or Exploratory]*	Domain	Sub-domain
The Newcastle Pediatric Mitochondrial Disease Scale	Supplemental – Highly Recommended	Outcomes and Endpoints	Pediatric
SF-36	Supplemental	Outcomes and Endpoints	Quality of Life

Case report forms (CRF) template *Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs*	Classification *[e.g., Core, Supplemental (also those highly-recommended), or Exploratory]*	Domain	Sub-domain
Echocardiogram	Supplemental–Highly Recommended	Assessments and Examinations	Exercise Physiology
Electrocardiogram	PR interval/QRS duration/QT interval–Supplemental Highly Recommended	Assessments and Examinations	Exercise Physiology
Holter Examination	Supplemental	Assessments and Examinations	Exercise Physiology
Maximal Exercise Test	Supplemental–Highly Recommended	Assessments and Examinations	Exercise Physiology
Mitochondrial Manifestations from NAMDC	Exploratory	Assessments and Examinations	Exercise Physiology
NAMDC Exercise Physiology Question	Exploratory	Assessments and Examinations	Exercise Physiology

Pulmonary Function	Supplemental Highly Recommended CDEs: Forced Vital Capacity Forced Vital Capacity Volume in 1 Second (FEV1)	Assessments and Examinations	Exercise Physiology
Sub-Maximal Exercise Test	Supplemental–Highly Recommended	Assessments and Examinations	Exercise Physiology
Two Dimensional Strain Echocardiography	Exploratory	Assessments and Examinations	Exercise Physiology
Laboratory Testing	Supplemental	Assessments and Examinations	Laboratory Findings
31-P Magnetic Resonance Spectroscopy	Exploratory	Imaging	Exercise Physiology
Cardiac Tagging Magnetic Resonance Imaging	Supplemental	Imaging	Exercise Physiology