MITOCHONDRIAL DISEASE BIOMARKERS		
EXERCISE TESTING		
CYCLE ERGOMETRY	THE CHARACTERIZATION OF EXERCISE INTOLERANCE IN MITOCHONDRIAL DISEASE IS PERFORMED USING CYCLE ERGOMETRY WITH MEASUREMENTS OF VO_2, VCO_2, RESPIRATORY EXCHANGE RATIO (RER = VCO_2/VO_2), HEART RATE, MINUTE VENTILATION, RATING OF PERCEIVED EXERTION, AND CARDIAC OUTPUT. EXERCISE PROTOCOLS TO MAXIMUM OR FOR A GIVEN TIME PERIOD AT A SET WORKLOAD CAN DIFFERENTIATE MITOCHONDRIAL DISEASE FROM CONTROLS WITH A SENSITIVITY OF APPROXIMATELY 0.63-0.75 AND A SPECIFICITY OF 0.70-0.90.	[1-6]
BLOOD (SERUM / PLASMA)		
LACTATE	LACTATE, THE PRODUCT OF ANAEROBIC GLUCOSE METABOLISM, ACCUMULATES WHEN AEROBIC METABOLISM IS IMPAIRED, WHICH CAUSES A SHIFT IN THE OXIDIZED-TO-REDUCED NAD_/ NADH RATIO WITHIN MITOCHONDRIA (IE, DECREASE IN THE OXIDIZED NICOTINAMIDE-ADENINE DINUCLEOTIDE/REDUCED NICOTINAMIDE-ADENINE DINUCLEOTIDE "REDOX" RATIO).NORMAL LACTATE DOES NOT EXCLUDE A MITOCHONDRIAL DISEASE, AND INCREASES IN LACTATE ARE NOT SPECIFIC TO THESE DISEASES. CAREFUL COLLECTION IS IMPORTANT SINCE A VARIETY OF DIFFICULTIES WITH COLLECTION INCLUDING PROLONGED TOURNIQUET USE AND STRUGGLING DURING BLOOD DRAW CAN ELEVATE LEVELS. SENSITIVITY AND SPECIFICITY FOR CONTROLS IS ESTIMATED TO BE APPROXIMATELY 5% AND 98%, RESPECTIVELY. NEGATIVE AND POSITIVE PREDICTIVE VALUES ARE ESTIMATED AT APPROXIMATELY 50% AND 77% RESPECTIVELY. SENSITIVITY AND SPECIFICITY FOR MITOCHONDRIAL DISEASE IS ESTIMATED TO BE APPROXIMATELY 15% AND 83%, RESPECTIVELY. NEGATIVE AND POSITIVE PREDICTIVE VALUES ARE ESTIMATED AT APPROXIMATELY 89% AND 59% RESPECTIVELY.	[7-10]
PYRUVATE	INCREASES IN PYRUVATE SIGNALS DYSFUNCTION OF THE CELLULAR OXIDATIVE PROCESS. NORMAL PYRUVATE DOES NOT EXCLUDE A MITOCHONDRIAL DISEASE, AND INCREASE IN PYRUVATE ARE NOT SPECIFIC TO THESE DISEASES. CAREFUL COLLECTION IS IMPORTANT SINCE A VARIETY OF DIFFICULTIES WITH COLLECTION INCLUDING PROLONGED TOURNIQUET USE AND STRUGGLING DURING BLOOD DRAW CAN ELEVATE LEVELS. SENSITIVITY AND SPECIFICITY FOR CONTROLS IS ESTIMATED TO BE APPROXIMATELY 40% AND 83%, RESPECTIVELY. NEGATIVE AND POSITIVE PREDICTIVE VALUES ARE ESTIMATED AT APPROXIMATELY 42% AND 81% RESPECTIVELY. SENSITIVITY AND SPECIFICITY FOR MITOCHONDRIAL DISEASE IS ESTIMATED TO BE APPROXIMATELY 34% AND 83%, RESPECTIVELY. NEGATIVE AND POSITIVE PREDICTIVE VALUES ARE ESTIMATED AT APPROXIMATELY 62% AND 61% RESPECTIVELY.	[7-10]
LACTATE / PYRUVATE RATIO	THE BLOOD LACTATE-TO-PYRUVATE (L:P) RATIO REFLECTS THE EQUILIBRIUM BETWEEN PRODUCT AND SUBSTRATE OF THE REACTION CATALYZED BY LACTATE DEHYDROGENASE. THE L:P RATIO IS CORRELATED WITH THE CYTOPLASMIC NADH:NAD^+ RATIO AND IS USED AS A MARKER OF THE REDOX STATE. WITH IMPAIRMENT OF CELLULAR RESPIRATION, PYRUVATE OXIDATION IS REDUCED, RESULTING IN AN INCREASE IN THE L:P RATIO. IN PYRUVATE DEHYDROGENASE DEFICIENCY (PDH DEFICIENTY), THE METABOLIC BLOCK IS UPSTREAM OF THE RESPIRATORY CHAIN. THE L:P RATIO IS NORMAL OR LOW. AN INCREASED L:P RATIO (>25) SUGGESTS PRIMARY OR SECONDARY RESPIRATORY CHAIN DYSFUNCTION. A RATIO <25 MAY INDICATE A PDH DEFECT IN THE APPROPRIATE CLINICAL SETTING. SENSITIVITY AND SPECIFICITY FOR CONTROLS IS ESTIMATED TO BE APPROXIMATELY 5% AND 98%, RESPECTIVELY. NEGATIVE AND POSITIVE PREDICTIVE VALUES ARE ESTIMATED AT APPROXIMATELY 50% AND 77% RESPECTIVELY. SENSITIVITY AND SPECIFICITY FOR MITOCHONDRIAL DISEASE IS ESTIMATED TO BE APPROXIMATELY 11% AND 98%, RESPECTIVELY. NEGATIVE AND POSITIVE PREDICTIVE VALUES ARE ESTIMATED AT APPROXIMATELY 86% AND 58% RESPECTIVELY.	[7-10]
AMINO ACIDS (EMPHASIS ON ALANINE, ALANINE / LYSINE RATIO, ALANINE / PHENYLALANINE + LYSINE RATIO, CITRULLINE)	ELEVATED ALANINE, GLYCINE, PROLINE, SARCOSINE, OR TYROSINE CAN BE OBSERVED IN MITOCHONDRIAL DISEASES. ELEVATED PLASMA ALANINE LEVELS, WHEN PRESENT, MAY BE A USEFUL INDICATOR OF LONG-STANDING PYRUVATE ACCUMULATION.	[7-9, 11]
CARNITINE LEVELS	CARNITINE PLAYS AN ESSENTIAL ROLE IN THE TRANSLOCATION OF LONG-CHAIN FATTY-ACIDS INTO THE MITOCHONDRIAL MATRIX FOR SUBSEQUENT BETA-OXIDATION, AND HAS A VITAL ROLE IN THE REGULATION OF BOTH FAT AND CARBOHYDRATE MUSCLE METABOLISM. FREE CARNITINE TENDS TO BE LOWER THAN NORMAL IN BLOOD OF PATIENTS WITH ETC DEFECTS, WHEREAS ESTERIFIED CARNITINE TENDS TO BE INCREASED. MEDICATIONS AND TOXINS CAN ALSO SIGNIFICANTLY AFFECT MITOCHONDRIAL FUNCTION SUCH AS VALPROATE WHICH CAN PRODUCE CARNITINE DEFICIENCY.	[7, 9]

Acylcarnitines	Carnitine plays an essential role in the transfer of long-chain fatty acids into the mitochondria for beta-oxidation. Carnitine binds acyl residues to enhance elimination. This mechanism is essential in removing abnormal organic acids in several organic acidemias and often causes secondary carnitine deficiencies. Secondary carnitine deficiencies can occur in mitochondrial diseases.	[7-9, 12]
CPK	Creatine kinase activity is greatest in striated muscle, heart tissue, and brain. The determination of CK activity is a commonly used assay in the investigation of skeletal muscle disease. Patients with mitochondrial disease can have increases in CPK or even episodes of rhabdomyolysis. Sensitivity and specificity for controls is estimated to be approximately 35% and 97%, respectively. Negative and positive predictive values are estimated at approximately 78% and 83% respectively. Sensitivity and specificity for mitochondrial disease is estimated to be approximately 22% and 97%, respectively. Negative and positive predictive values are estimated at approximately 86% and 60% respectively.	[7, 8, 10]
Creatine	The concentration of creatine is linked to the concentration of phosphocreatine (PCr) through the Cr kinase reaction, whose kinetics are influenced by the balance between mitochondrial oxidative phosphorylation activity and ATP demand. Elevation of plasma creatine in RCD patients signals a low energetic state of tissues using the phosphocreatine shuttle.	[13]
Free glutathione (fGSH), oxidized disulfide (GSSG), fGSH/GSSG ratio	Glutathione (GSH) is the main non-protein thiol in cells. GSH functions are dependent on the redox-active thiol of its cysteine moiety that serves as a cofactor for a number of antioxidant and detoxifying enzymes. While synthesized exclusively in the cytosol from its constituent amino acids, GSH is distributed in different compartments, including mitochondria where its concentration in the matrix equals that of the cytosol. Free GSH/GSSG ratio is an indicator of redox metabolism (oxidative stress marker). Glutathione decreases in mitochondrial disease.	[11, 14, 15]
Plasma carbonyl content	protein carbonyls are primarily produced as a result of ROS mediated protein damage and may also be caused by reactive aldehyde intermediates of organic acids. Protein carbonyls are markers for oxidative protein damage. Increases can be observed in mitochondrial diseases.	[11]
Fibroblast growth factor 21 (FGF21)	Mitochondrial diseases produce a transcriptional response mimicking starvation which includes increased expression of the metabolic regulator fgf21. Sensitivity and specificity for controls is estimated to be approximately 35% and 95%, respectively. Negative and positive predictive values are estimated at approximately 70% and 83% respectively. Sensitivity and specificity for mitochondrial disease is estimated to be approximately 66% and 95%, respectively. Negative and positive predictive values are estimated at approximately 92% and 78% respectively. FGF-21 is known to be increased in a wide range of metabolic disorders such as diabetes, obesity, and the metabolic syndrome.	[10, 16-23]
Growth Differentiation factor – 15 (GDF-15)	Growth differentiation factor 15 (GDF-15), a member of the transforming growth factor beta superfamily, has been proposed as a useful biomarker for mitochondrial disorders. Sensitivity and specificity for disease control is estimated to be 98% (vs. 77% in FGF-21) and 52% (vs. 79% in FGF-21), respectively. Sensitivity and specificity for mitochondrial disease is estimated to be 98% (vs. 77% in FGF-21) and 86% (vs. 86% in FGF-21) 7. GDF-15 is known to be increased in cardiac failure, renal insufficiency and prostate cancer.	[172-173]
Metabolic profiling	Metabolic profiling provides information on consumption and secretion of metabolic intermediates. This method assesses a wide biochemical spectrum including amino acids, organic acids, nucleotides, and sugars, enabling simultaneous monitoring of multiple metabolic pathways. Metabolic profiling is performed by LC-MS/MS in culture media. plasma measurements of mitochondrial dysfunction; correlates with extracellular metabolic profile in myotubes (See below).	[13]
Hepatic enzymes (AST, ALT, GGT)	Aspartate aminotransferase (AST) is found in high concentrations in liver, heart, skeletal muscle and kidney. AST is present in both cytoplasm and mitochondria of cells. Alanine aminotransferase (ALT) is present primarily in liver cells. In viral hepatitis and other forms of liver disease associated with hepatic necrosis, serum ALT is elevated even before the clinical signs and	[8]

	symptoms of the disease appear. Gamma-glutamyltransferase (GGT) is primarily present in kidney, liver, and pancreatic cells. Some mitochondrial diseases have hepatic involvement that can be mild to severe. In some patients hepatic failure occurs (e.g Alper disease).	
Ammonia	Hyperammonemia can occur when there is impaired capacity of the body to excrete nitrogenous waste. Ammonia is elevated in the following conditions: liver disease, urinary tract infection with distention and stasis, Reye syndrome, inborn errors of metabolism including deficiency of enzymes in the urea cycle, HHH syndrome (hyperammonemia-homocitrullinuria, hyperornithinemia), some normal neonates (usually returning to normal in 48 hours), total parenteral nutrition, ureterosigmoidostomy, and sodium valproate therapy. Some mitochondrial diseases have hepatic involvement that can be mild to severe. In some patients hepatic failure occurs (e.g Alper disease).	[8]
Thymidine	A group of mitochondrial diseases are caused by mutations in genes that encode proteins that maintain the mitochondrial dNTP pool. These mutations cause an accumulation of thymidine and deoxyuridine, leading to an imbalance of cytosolic dNTP pools. Because the mitochondrial dNTP pool relies, in part, on dNTP imported from the cytosol, an imbalanced cytosolic dNTP pool can lead to an imbalanced mitochondrial dNTP pool that can impair mtDNA synthesis.	[24, 25]
Deoxyuridine	A group of mitochondrial diseases are caused by mutations in genes that encode proteins that maintain the mitochondrial dNTP pool. These mutations cause an accumulation of thymidine and deoxyuridine, leading to an imbalance of cytosolic dNTP pools. Because the mitochondrial dNTP pool relies, in part, on dNTP imported from the cytosol, an imbalanced cytosolic dNTP pool can lead to an imbalanced mitochondrial dNTP pool that can impair mtDNA synthesis.	[24, 25]
Urine		
Organic acids	Urine organic acid testing is useful in the diagnosis and monitoring of patients with inborn errors of organic acid metabolism, inborn errors of amino acid metabolism, urea cycle defects, and defects of the mitochondrial respiratory chain. Organic acid analysis may fail to detect certain disorders that are characterized by minimal or intermittent metabolite excretion. Metabolic changes observed in mitochondrial diseases include increased levels of TCA intermediates, lactate, pyruvate, 3-methylglutaconic acid).	[7, 8, 26]
3-methylglutaconic acid	The branched-chain organic acid 3-methylglutaconic acid (3-MGA) is an intermediate of the mitochondrial leucine catabolism. However, in mitochondrial diseases, 3-MGA is a biochemical marker for mitochondrial dysfunction of still unknown origin.	[27, 28]
Amino acids	Elevated alanine, glycine, proline, sarcosine, or tyrosine can be observed in mitochondrial diseases. Elevated plasma alanine levels, when present, may be a useful indicator of long-standing pyruvate accumulation. Urine amino acids may also detect proximal renal tubule dysfunction leading to a generalized aminoaciduria.	[7, 8]
CSF		
lactate	Lactate concentrations in CSF result from a complex balance between efflux and influx through the blood–brain barrier and through the plasma membrane of central nervous system cells. CSF lactate concentrations were more sensitive for mitochondrial disorders than are blood lactate concentrations. Lactate is increased with oxidative phosphorylation defects. Both pyruvate and lactate concentrations are increased in PDH deficiency, but the L/P ratio remains normal or only slightly decreased. Lactate is reported to have a sensitivity of 73%, specificity of 97%, positive predictive value of 65% and negative predictive value of 93%. Even when plasma levels of lactate and pyruvate are normal, cerebrospinal fluid (CSF) lactate levels may be elevated in patients with mitochondrial disease who have predominant brain manifestations.	[7, 8] [29]
pyruvate	Pyruvic acid, an intermediate metabolite, plays an important role in linking carbohydrate and amino acid metabolism to the tricarboxylic acid cycle, the fatty acid beta-oxidation pathway, and the mitochondrial respiratory chain complex.Pyruvate is reported to have a sensitivity of 42%, specificity of 97%,	[7, 8] [29]

	positive predictive value of 79% and negative predictive value of 96%. Even when plasma levels of lactate and pyruvate are normal, cerebrospinal fluid (CSF) lactate levels may be elevated in patients with mitochondrial disease who have predominant brain manifestations.	
latate / pyruvate ratio	The CSF lactate-to-pyruvate (L:P) ratio reflects the equilibrium between product and substrate of the reaction catalyzed by lactate dehydrogenase. The L:P ratio is correlated with the cytoplasmic NADH:NAD^+ ratio and is used as a marker of the redox state. With impairment of cellular respiration, pyruvate oxidation is reduced and lactate is increased, resulting in an increase in the L:P ratio. In pyruvate dehydrogenase deficiency (PDH deficienty), the metabolic block is upstream of the respiratory chain. Both pyruvate and lactate concentrations are increased in PDH deficiency, but the L/P ratio remains normal or only slightly decreased. An increased L:P ratio (>25) suggests primary or secondary respiratory chain dysfunction. A ratio <25 may indicate a PDH defect in the appropriate clinical setting. The Lactate/Pyruvate ratio is reported to have a sensitivity of 31%, specificity of 97%, positive predictive value of 62% and negative predictive value of 91%. Even when plasma levels of lactate and pyruvate are normal, cerebrospinal fluid (CSF) lactate levels may be elevated in patients with mitochondrial disease who have predominant brain manifestations.	[29]
Amino acids (alanine, alanine / lysine ratio, alanine / phenylalanine + lysine ratio)	Elevated alanine, glycine, proline, sarcosine, or tyrosine can be observed in mitochondrial diseases. Elevated plasma alanine levels, when present, may be a useful indicator of long-standing pyruvate accumulation.	[7, 8]
Cell count	Cell count can be helpful in assessing then metabolic parameters by assessing for increases in red blood cells due to traumatic spinal tap.	[8]
Protein	Cerebrospinal fluid (CSF) is secreted by the choroid plexuses, around the cerebral vessels, and along the walls of the ventricles of the brain. CSF turnover is rapid, exchanging about four times per day. More than 80% of CSF protein content originates from plasma by ultrafiltration through the walls of capillaries in the meninges and choroid plexuses; the remainder originates from intrathecal synthesis. Increases are observed in some disorders such as Leigh disease, Alper syndrome, and Kearns-Sayre sydrome.	[8]
Glucose (with simultaneous blood glucose)	CSF glucose levels may be decreased due to consumption by microorganisms, impaired glucose transport, or increased glycolysis. CSF glucose is normal in most mitochondrial diseases. GLUT1 deficiency syndrome is a treatable neurometabolic disorder, characterized by a low concentration of glucose in cerebrospinal fluid (CSF) and a decreased CSF to blood glucose ratio. This decrease in CSF glucose limits ATP generation by cellular energetics.	[8, 30]
Growth differentiation factor – 15 (GDF-15)	Growth differentiation factor 15 (GDF-15), a member of the transforming growth factor beta superfamily, has been proposed as a useful biomarker for mitochondrial disorders. It is also excreted in the CSF which is reflected by the serum level in mitochondrial disorders. Sensitivity and specificity for disease control is estimated to be 98% and 52%, respectively. Sensitivity and specificity for mitochondrial disease is estimated to be 98% and 86%. GDF-15 is known to be increased in cardiac failure, renal insufficiency, and prostate cancer.	[172-173]
Fibroblasts		
high resolution respirometry	Live cellular respiration (complexes I-V) allows measurement of parameters such as mitochondrial membrane potential, reserve capacity for ATP generation, and complex I-IV substrate utilization. This testing assesses functional characteristics of intact mitochondria within living tissues.	[31, 32]
OXPHOS enzymology	OXPHOS enzymology assesses mitochondrial function by determining maximal enzymatic activity of the individual electron transport system (ETS) complexes in disrupted mitochondria by spectrophotometry. However, many aspects of mitochondrial function that occur in live cells cannot be assessed by OXPHOS enzymology.	[32]
Lactate /pyruvate ratio	The fibroblast lactate-to-pyruvate (L:P) ratio reflects the equilibrium between product and substrate of the reaction catalyzed by lactate dehydrogenase. The L:P ratio is correlated with the cytoplasmic NADH:NAD^+ ratio and is used as a marker of the redox state. With impairment of cellular respiration, pyruvate oxidation is reduced and lactate is increased, resulting	[31]

	in an increase in the L:P ratio. In pyruvate dehydrogenase deficiency (PDH deficienty), the metabolic block is upstream of the respiratory chain. Both pyruvate and lactate concentrations are increased in PDH deficiency, but the L/P ratio remains normal or only slightly decreased.	
Pyruvate dehydrogenase enzymology	The mitochondrial pyruvate dehydrogenase complex (PDC) catalyzes the rate-limiting step in the aerobic glucose oxidation and is thus integral to cellular energetics. Pyruvate dehydrogenase (PDH) deficiency is an inherited disorder of carbohydrate metabolism. PDH deficiency is due to loss-of-function mutation in one of the five component enzymes, most commonly E1a-subunit. The common clinical presentation ranges from fatal infantile lactic acidosis in newborns to chronic neurological dysfunction. Pyruvate dehydrogenase specific activity is typically determined by measuring the decarboxylation of 1-^{14}C-pyruvate to $^{14}CO_2$ and was expressed as a unit of $^{14}CO_2$ production per tissue mass per unit of time.	[33, 34]
Pyruvate dehydrogenase subunit western blot	Western blotting of denatured subunits of pyruvate dehydrogenase allow recognition of pyruvate dehydrogenase deficiencies when a subunit is decreased, missing or of abnormal molecular weight. Western blotting is more amenable to protein quantitation and offers the additional ability to confirm molecular identity of the target protein by molecular weight.	[35]
Pyruvate dehydrogenase immunohistochemistry	Immunohistochemistry can be used for the analysis of very small numbers of cells and is particularly well-suited to the analysis of cultured cells, where cellular individuality can be assessed with confidence and cell population mosaicism can be detected. Defects causing decreases or absences of subunits can be detected.	[35]
ATP synthesis		[36]
Fibroblast OXPHOS subunit immunohistochemistry	Immunohistochemistry can be used for the analysis of very small numbers of cells and is particularly well-suited to the analysis of cultured cells, where cellular individuality can be assessed with confidence and cell population mosaicism can be detected. Defects causing decreases or absences of subunits can be detected.	[37]
OXPHOS subunit western blot	Western blotting of denatured selected subunits of OXPHOS enzymes allows recognition of defects causing a subunit to be decreased, missing or of abnormal molecular weight. Western blotting is more amenable to protein quantitation and offers the additional ability to confirm molecular identity of the target protein by molecular weight.	
Blue native gel electrophoresis (OXPHOS)	Clear native electrophoresis and blue native electrophoresis are microscale techniques for the isolation of membrane protein complexes. Proteins are visualized in Blue Native gels with Coomassie Blue G-250 dye. Blue Native-PAGE retains enzyme complexes in their intact and enzymatically active form. Both the amount of the fully assembled complex, and the presence of any smaller stalled assembly intermediates, can then be determined.	[38, 39]
Clear native gel OXPHOS immunoblot	Clear Native Gel electrophoresis retains enzyme complexes in their intact and enzymatically active form. Both the amount of the fully assembled complex, and the presence of any smaller stalled assembly intermediates, can then be determined by immunoblotting using one or more subunit antibodies.	[39]
Clear native gel OXPHOS enzymology	Clear Native Gel electrophoresis retains enzyme complexes in their intact and enzymatically active form. Both the amount of the fully assembled complex, and the presence of any smaller stalled assembly intermediates, can then be determined by assessing the enzyme activity of each OXPHOS enzyme.	[39]
Coenzyme Q10	Coenzyme Q10 deficiency	[40-43]
Leukocytes		
Intracellular free glutathione (fGSH), oxidized disulfide (GSSG), fGSH/GSSG ratio	Glutathione (GSH) is the main non-protein thiol in cells. GSH functions are dependent on the redox-active thiol of its cysteine moiety that serves as a cofactor for a number of antioxidant and detoxifying enzymes. While synthesized exclusively in the cytosol from its constituent amino acids, GSH is distributed in different compartments, including mitochondria where its concentration in the matrix equals that of the cytosol. Free GSH/GSSG ratio is an indicator of redox metabolism (oxidative stress marker). Glutathione decreases in mitochondrial disease.	[11]
Intracellular coenzyme Q10		[44]

Pyruvate Dehydrogenase Enzymology	The mitochondrial pyruvate dehydrogenase complex (PDC) catalyzes the rate-limiting step in the aerobic glucose oxidation and is thus integral to cellular energetics. Pyruvate dehydrogenase (PDH) deficiency is an inherited disorder of carbohydrate metabolism. PDH deficiency is due to loss-of-function mutation in one of the five component enzymes, most commonly E1a-subunit. The common clinical presentation ranges from fatal infantile lactic acidosis in newborns to chronic neurological dysfunction. Pyruvate dehydrogenase specific activity is typically determined by measuring the decarboxylation of 1-^{14}C-pyruvate to $^{14}CO_2$ and was expressed as a unit of $^{14}CO_2$ production per tissue mass per unit of time.	
Thymidine phosphorylase enzymology		[24, 25]
Coenzyme Q10 level	Coenzyme Q10 deficiency	[45]
Neutrophils		
OXPHOS enzymology	OXPHOS enzymology assesses mitochondrial function by determining maximal enzymatic activity of the individual electron transport system (ETS) complexes in disrupted mitochondria by spectrophotometry. However, many aspects of mitochondrial function that occur in live cells cannot be assessed by OXPHOS enzymology.	[46]
High resolution respirometry	Live cellular respiration (complexes I-V) allows measurement of parameters such as mitochondrial membrane potential, reserve capacity for ATP generation, and complex I-IV substrate utilization. This testing assesses functional characteristics of intact mitochondria within living tissues.	[46]
Coenzyme Q10	coenzyme q10 deficiency	[46]
Intracellular glutathione	Glutathione (GSH) is the main non-protein thiol in cells. GSH functions are dependent on the redox-active thiol of its cysteine moiety that serves as a cofactor for a number of antioxidant and detoxifying enzymes. While synthesized exclusively in the cytosol from its constituent amino acids, GSH is distributed in different compartments, including mitochondria where its concentration in the matrix equals that of the cytosol. Glutathione decreases in mitochondrial disease.	[11]
Leukocytes/Monocytes		
Intracellular free glutathione (fGSH), oxidized disulfide (GSSG), fGSH/GSSG ratio	Glutathione (GSH) is the main non-protein thiol in cells. GSH functions are dependent on the redox-active thiol of its cysteine moiety that serves as a cofactor for a number of antioxidant and detoxifying enzymes. While synthesized exclusively in the cytosol from its constituent amino acids, GSH is distributed in different compartments, including mitochondria where its concentration in the matrix equals that of the cytosol. Free GSH/GSSG ratio is an indicator of redox metabolism (oxidative stress marker). Glutathione decreases in mitochondrial disease.	[11]
Pyruvate Dehydrogenase Enzymology	The mitochondrial pyruvate dehydrogenase complex (PDC) catalyzes the rate-limiting step in the aerobic glucose oxidation and is thus integral to cellular energetics. Pyruvate dehydrogenase (PDH) deficiency is an inherited disorder of carbohydrate metabolism. PDH deficiency is due to loss-of-function mutation in one of the five component enzymes, most commonly E1a-subunit. The common clinical presentation ranges from fatal infantile lactic acidosis in newborns to chronic neurological dysfunction. Pyruvate dehydrogenase specific activity is typically determined by measuring the decarboxylation of 1-^{14}C-pyruvate to $^{14}CO_2$ and was expressed as a unit of $^{14}CO_2$ production per tissue mass per unit of time.	
Thymidine phosphorylase enzymology		[24, 25]
OXPHOS enzymology	OXPHOS enzymology assesses mitochondrial function by determining maximal enzymatic activity of the individual electron transport system (ETS) complexes in disrupted mitochondria by spectrophotometry. However, many aspects of mitochondrial function that occur in live cells cannot be assessed by OXPHOS enzymology.	[46]
High resolution respirometry	Live cellular respiration (complexes I-V) allows measurement of parameters such as mitochondrial membrane potential, reserve capacity for ATP generation, and complex I-IV substrate utilization. This testing assesses functional characteristics of intact mitochondria within living tissues.	[46]
Coenzyme Q10	Inherited coenzyme Q10 deficiency is a potentially treatable mitochondrial disease. Coenzyme q10 levels in skeletal muscle correlate better with	[44-46]

	monocyte CoQ10 levels than plasma CoQ10 levels.	
Intracellular glutathione	Glutathione (GSH) is the main non-protein thiol in cells. GSH functions are dependent on the redox-active thiol of its cysteine moiety that serves as a cofactor for a number of antioxidant and detoxifying enzymes. While synthesized exclusively in the cytosol from its constituent amino acids, GSH is distributed in different compartments, including mitochondria where its concentration in the matrix equals that of the cytosol. Glutathione decreases in mitochondrial disease.	[11]
Platelets (high oxphos)		
OXPHOS enzymology	OXPHOS enzymology assesses mitochondrial function by determining maximal enzymatic activity of the individual electron transport system (ETS) complexes in disrupted mitochondria by spectrophotometry. However, many aspects of mitochondrial function that occur in live cells cannot be assessed by OXPHOS enzymology.	[46]
High resolution respirometry	Live cellular respiration (complexes I-V) allows measurement of parameters such as mitochondrial membrane potential, reserve capacity for ATP generation, and complex I-IV substrate utilization. This testing assesses functional characteristics of intact mitochondria within living tissues.	[46, 47]
coenzyme Q10	coenzyme q10 deficiency	[46]
peripheral-type benzodiazepine receptor binding kinetics	kinetic binding parameters of PBR are altered in mitochondrial disease	[48]
Lymphocytes (highest oxphos)		
OXPHOS enzymology	OXPHOS enzymology assesses mitochondrial function by determining maximal enzymatic activity of the individual electron transport system (ETS) complexes in disrupted mitochondria by spectrophotometry. However, many aspects of mitochondrial function that occur in live cells cannot be assessed by OXPHOS enzymology.	[46]
high resolution respirometry	Live cellular respiration (complexes I-V) allows measurement of parameters such as mitochondrial membrane potential, reserve capacity for ATP generation, and complex I-IV substrate utilization. This testing assesses functional characteristics of intact mitochondria within living tissues.	[46]
coenzyme Q10	coenzyme q10 deficiency	[46]
Intracellular glutathione	Glutathione (GSH) is the main non-protein thiol in cells. GSH functions are dependent on the redox-active thiol of its cysteine moiety that serves as a cofactor for a number of antioxidant and detoxifying enzymes. While synthesized exclusively in the cytosol from its constituent amino acids, GSH is distributed in different compartments, including mitochondria where its concentration in the matrix equals that of the cytosol. Glutathione decreases in mitochondrial disease.	[11]
DNA strand breaks by Comet assay (cultured cells)	single cell gel electrophoresis which estimates levels of primary and oxidative DNA damage	[49, 50]
Micronucleus assay followed by fluorescence in situ hybridisation	chromosome damage in peripheral blood lymphocytes in mitochondrial disease; cytokinesis block micronucleus method in cultured peripheral blood lymphocytes, coupled with fluorescence in situ hybridization analysis using a digoxigenin-labelled pancentromeric DNA probe	[50, 51]
Pyruvate dehydrogenase	The mitochondrial pyruvate dehydrogenase complex (PDC) catalyzes the rate-limiting step in the aerobic glucose oxidation and is thus integral to cellular energetics. Pyruvate dehydrogenase (PDH) deficiency is an inherited disorder of carbohydrate metabolism. PDH deficiency is due to loss-of-function mutation in one of the five component enzymes, most commonly E1a-subunit. The common clinical presentation ranges from fatal infantile lactic acidosis in newborns to chronic neurological dysfunction. Pyruvate dehydrogenase specific activity is typically determined by measuring the decarboxylation of 1-^{14}C-pyruvate to $^{14}CO_2$ and was expressed as a unit of $^{14}CO_2$ production per tissue mass per unit of time.	[52, 53]
Lymphoblasts (EBV transformed)		
ATP synthesis		[54]
High resolution respirometry	Live cellular respiration (complexes I-V) allows measurement of parameters such as mitochondrial membrane potential, reserve capacity for ATP generation, and complex I-IV substrate utilization. This testing assesses functional characteristics of intact mitochondria within living tissues.	[54]

Muscle Biochemistry		
OXPHOS enzymology	OXPHOS enzymology assesses mitochondrial function by determining maximal enzymatic activity of the individual electron transport system (ETS) complexes in disrupted mitochondria by spectrophotometry. However, many aspects of mitochondrial function that occur in live cells cannot be assessed by OXPHOS enzymology.	[32]
high resolution respirometry	live cellular respiration (complexes I-V) allows measurement of parameters such as mitochondrial membrane potential, reserve capacity for ATP generation, and complex I-IV substrate utilization. This testing assesses functional characteristics of intact mitochondria within living tissues.	
mtDNA copy number	mtDNA depletion	
mtDNA deletion/duplication	mtDNA deletion disorders; somatic mutations	
Pyruvate dehydrogenase enzymology	The mitochondrial pyruvate dehydrogenase complex (PDC) catalyzes the rate-limiting step in the aerobic glucose oxidation and is thus integral to cellular energetics. Pyruvate dehydrogenase (PDH) deficiency is an inherited disorder of carbohydrate metabolism. PDH deficiency is due to loss-of-function mutation in one of the five component enzymes, most commonly E1a-subunit. The common clinical presentation ranges from fatal infantile lactic acidosis in newborns to chronic neurological dysfunction. Pyruvate dehydrogenase specific activity is typically determined by measuring the decarboxylation of 1-^{14}C-pyruvate to $^{14}CO_2$ and was expressed as a unit of $^{14}CO_2$ production per tissue mass per unit of time.	[34, 55]
Pyruvate dehydrogenase subunit western blot	Western blotting of denatured subunits of pyruvate dehydrogenase allow recognition of pyruvate dehydrogenase deficiencies when a subunit is decreased, missing or of abnormal molecular weight. Western blotting is more amenable to protein quantitation and offers the additional ability to confirm molecular identity of the target protein by molecular weight.	[35]
Coenzyme Q10	Coenzyme Q10 deficiency	[40, 41]
Glutathione	Glutathione (GSH) is the main non-protein thiol in cells. GSH functions are dependent on the redox-active thiol of its cysteine moiety that serves as a cofactor for a number of antioxidant and detoxifying enzymes. While synthesized exclusively in the cytosol from its constituent amino acids, GSH is distributed in different compartments, including mitochondria where its concentration in the matrix equals that of the cytosol. Glutathione decreases in mitochondrial disease.	[56]
OXPHOS subunit western blot	Western blotting of denatured selected subunits of OXPHOS enzymes allows recognition of defects causing a subunit to be decreased, missing or of abnormal molecular weight. Western blotting is more amenable to protein quantitation and offers the additional ability to confirm molecular identity of the target protein by molecular weight.	[57]
Blue native gel electrophoresis (OXPHOS)	Clear native electrophoresis and blue native electrophoresis are microscale techniques for the isolation of membrane protein complexes. Proteins are visualized in Blue Native gels with Coomassie Blue G-250 dye. Blue Native-PAGE retains enzyme complexes in their intact and enzymatically active form. Both the amount of the fully assembled complex, and the presence of any smaller stalled assembly intermediates, can then be determined.	[38, 39, 58-62]
Clear native gel OXPHOS immunoblot	Clear Native Gel electrophoresis retains enzyme complexes in their intact and enzymatically active form. Both the amount of the fully assembled complex, and the presence of any smaller stalled assembly intermediates, can then be determined by immunoblotting using one or more subunit antibodies.	[39, 63]
Clear native gel OXPHOS enzymology	Clear Native Gel electrophoresis retains enzyme complexes in their intact and enzymatically active form. Both the amount of the fully assembled complex, and the presence of any smaller stalled assembly intermediates, can then be determined by assessing the enzyme activity of each OXPHOS enzyme.	[39, 64-67]
Human mitochondrial transcription factor A (hmtTFA or Tfam)	involved in the control of replication and transcription of mtDNA; h-mtTFA levels are significantly inversely related to blood lactate and the percent of RRF, cox deficient fibers	[68]
mitochondrial DNA absence sensitive factor) (MIDAS)	expression was enhanced by the absence of mitochondrial DNA	[69]
biogenesis regulator peroxisome	dramatically induce both nuclear and mitochondrial gene expression;	[70]

PROLIFERATOR-ACTIVATED RECEPTOR-GAMMA COACTIVATOR-1ALPHA (PGC-1ALPHA)	INCREASED IN MITOCHONDRIAL DISEASE	
8-OXOGUANINE DNA GLYCOLASE-1 (OGG-1)	OXIDATIVE-INDUCED LESIONS TO MTDNA CAN BE REPAIRED BY THE DNA REPAIR ENZYME 8-OXOGUANINE DNA GLYCOLASE-1; INCREASED IN MITOCHONDRIAL DISEASE	[70]
MANGANESE SUPEROXIDE DISMUTASE (MNSOD)	ROS ARE DETOXIFIED BY ANTIOXIDANT ENZYMES WITHIN THE MITOCHONDRION, SUCH AS MANGANESE SUPEROXIDE DISMUTASE (MNSOD); INCREASED IN MITOCHONDRIAL DISEASE	[70]
AIF	APOPTOTIC PROTEIN; ROS PROMOTE THE RELEASE OF APOPTOSIS-INDUCING FACTOR (AIF) AND CYTOCHROME C BY INDUCING MITOCHONDRIAL PERMEABILITY TRANSITION PORE (MTPTP) OPENING; INCREASED IN MITOCHONDRIAL DISEASE	[70]
BCL-2	APOPTOTIC PROTEIN; ROS PROMOTE THE RELEASE OF APOPTOSIS-INDUCING FACTOR (AIF) AND CYTOCHROME C BY INDUCING MITOCHONDRIAL PERMEABILITY TRANSITION PORE (MTPTP) OPENING. THE CONFORMATION OF THE MTPTP IS REGULATED BY THE BCL-2 FAMILY OF PROTEINS CONSISTING OF BOTH PRO- (I.E., BAX) AND ANTIAPOPTOTIC MEMBERS (I.E., BCL-2) IN THE OUTER MEMBRANE OF THE MITOCHONDRION; INCREASED IN MITOCHONDRIAL DISEASE	[70]
ACONITASE ENZYMOLOGY	TCA CYCLE ENZYME, DECREASED IN MITOCHONDRIAL DISEASE	[70]
MUSCLE HISTOLOGY		
GOMORI TRICHROME	RAGGED RED FIBERS	[71]
SUCCINATE DEHYDROGENASE (SDH)	COMPLEX II	[71]
CYCTOCHROME C OXIDASE (COX) (COMPLEX IV)	COMPLEX IV (COX DEFICIENCY)	[71]
COMBINED SDH + COX	COX DEFICIENCY, INCREASED SDH (MELAS)	[72]
FIBROBLAST GROWTH FACTOR 21 (FGF21)	MITOCHONDRIAL DISEASES PRODUCE A TRANSCRIPTIONAL RESPONSE MIMICKING STARVATION WHICH INCLUDES INCREASED EXPRESSION OF THE METABOLIC REGULATOR FGF21	[10, 21, 23]
OXPHOS SUBUNIT IMMUNOHISTOCHEMISTRY	IMMUNOHISTOCHEMISTRY CAN BE USED FOR THE ANALYSIS OF VERY SMALL NUMBERS OF CELLS AND IS PARTICULARLY WELL-SUITED TO THE ANALYSIS OF CULTURED CELLS, WHERE CELLULAR INDIVIDUALITY CAN BE ASSESSED WITH CONFIDENCE AND CELL POPULATION MOSAICISM CAN BE DETECTED. DEFECTS CAUSING DECREASES OR ABSENCES OF SUBUNITS CAN BE DETECTED.	[71, 73]
HUMANIN IMMUNOHISTOCHEMISTRY	HUMANIN IS AN ENDOGENOUS PEPTIDE THAT INCREASES CELLULAR ATP. IT IS INCREASED IN RAGGED RED/COX DEFICIENT FIBERS. IMMUNOHISTOCHEMISTRY CAN BE USED FOR THE ANALYSIS OF VERY SMALL NUMBERS OF CELLS AND IS PARTICULARLY WELL-SUITED TO THE ANALYSIS OF CULTURED CELLS, WHERE CELLULAR INDIVIDUALITY CAN BE ASSESSED WITH CONFIDENCE AND CELL POPULATION MOSAICISM CAN BE DETECTED. DEFECTS CAUSING DECREASES OR ABSENCES OF SUBUNITS CAN BE DETECTED.	[74]
MYOTUBES		
METABOLIC PROFILING	LC-MS/MS IN CULTURE MEDIA. EXTRACELLULAR METABOLIC PROFILE OF MITOCHONDRIAL DYSFUNCTION; CORRELATES WITH PLASMA MEASUREMENTS.	[13]
HIGH RESOLUTION RESPIROMETRY	LIVE CELLULAR RESPIRATION (COMPLEXES I-V) ALLOWS MEASUREMENT OF PARAMETERS SUCH AS MITOCHONDRIAL MEMBRANE POTENTIAL, RESERVE CAPACITY FOR ATP GENERATION, AND COMPLEX I-IV SUBSTRATE UTILIZATION. THIS TESTING ASSESSES FUNCTIONAL CHARACTERISTICS OF INTACT MITOCHONDRIA WITHIN LIVING TISSUES.	[13]
GENETIC		
CELLULAR ENERGETICS GENE SEQUENCING (NGS) (NDNA + MTDNA)	EXON + EXON/INTRON BOUNDARY SEQUENCING OF GENES RELATED TO CELLULAR ENERGETICS FUNCTION	[75-77]
MTDNA SEQUENCING		
EXOME SEQUENCING (NGS) (NDNA)		[75, 78-162]
MTDNA DELETION/DUPLICATION (LEUKOCYTES)	MTDNA DELETION DISORDERS; SOMATIC MUTATIONS	[163]
MTDNA DELETION/DUPLICATION (MUSCLE)	MTDNA DELETION DISORDERS; SOMATIC MUTATIONS	[163]
MTDNA COPY NUMBER (LEUKOCYTES)	MTDNA DEPLETION AND MTDNA INCREASES	[164, 165]
MTDNA COPY NUMBER (MUSCLE)	MTDNA DEPLETION AND MTDNA INCREASES	[163]
MITOCHONDRIAL HAPLOTYPE	EVOLUTIONARILY RELATED HAPLOTYPE GROUPS AND PHENOTYPIC CHARACTERISTICS	[166, 167]
MITOCHONDRIAL GENE EXPRESSION PROFILING		[168-171]

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