UNIVERSITY OF CALIFORNIA IRVINE
CONSENT TO ACT AS A HUMAN RESEARCH SUBJECT

Mitochondrial Inborn Errors of Metabolism and ANT Defects in Mitochondrial Diseases; A Master Protocol

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If I am the parent or legally authorized representative of a child under 16 years of age, "I" refers to "my child" and the remainder of the consent is addressed to me. If I am the parent of a neonate (Newborn child), "I" refers to "my newborn," and the remainder of the consent is addressed to me.

NAME OF SUBJECT: _____, DATE _____

PURPOSE OF STUDY:

I have been asked to volunteer for a medical research study which will explore the causes and inheritance of mitochondrial disease. While there is no guarantee that my participation will be of benefit to me or others, this study has the potential of helping develop more effective diagnostic tools and therapeutic regimes for mitochondrial diseases some time in the future.

The mitochondria are the power plants of the cell, providing most of the energy required for our daily activities. Like all power plants, the mitochondria also generate toxic by-products (the cellular equivalent of smoke) in the form of oxygen radicals. Defects in mitochondrial energy production not only diminish the energy available to our cells (the medical equivalent to a metropolitan brownout) but also increase the production and thus toxicity of oxygen radicals. Ultimately the energy level gets so low and the toxicity of the radicals sufficiently high that the cell malfunctions and may even die with resulting symptoms. In humans, any organ can be affected by mitochondrial disease. However, the organs most commonly seen to be affected are the brain, heart, muscle, kidney, liver and hormonal tissues.

Depending on the nature of my medical condition, my requested participation might range from involving mildly invasive techniques such as providing a blood sample to moderately invasive procedures such as providing a muscle biopsy and/or cerebrospinal fluid. The relationship between my problem and the proposed study and the degree of involvement requested of me will be explained so that I can make an informed decision as to whether to participate.

If I am a mitochondrial disease patient or relevant relative, many of the procedures in which I will be invited to participate are part of the standard-of-care procedures routinely used for the clinical evaluation and diagnosis of mitochondrial disease. These procedures will be indicated to me and billed to me or my insurance carrier as fee-for-service procedures. However, additional procedures may also be applicable to my case which goes beyond standard-of-care. These procedures and investigations will fall under research and will be provided to me free of charge. Evaluations that are being undertaken exclusively for research purposes will be free. This informed consent form will clearly indicate to me those procedures which fall into these two categories, fee-for-service or free for research so that I can make an informed decision as to whether or not to participate.

My participation is in this study is completely voluntary and my decision whether or not to participate in this study will in no way prejudice my receiving the standard-of-care procedures as outlined during my clinical evaluation.

SUBJECTS:

I will be eligible to participate if I, or a family member, have been clinically diagnosed with possible mitochondrial disorders. This study will include approximately 300 subjects which will be studied at the Center for Molecular and Mitochondrial Medicine and Genetics (C-MAMMAG) at UCI. I may also participate in this study if I am pregnant but the procedures I am invited to participate in are limited to those which only pose minimal risk to the fetus. Please note that this study is not designed to aid in prenatal diagnosis for mitochondrial disorders in any way since this is beyond the scope of this protocol. Pregnant women, seeking prenatal diagnosis through the study team are not eligible for this protocol.

PROCEDURES:

The procedures listed below represent an array of possible tests in which I might be asked to participate. Those procedures that will be required for my evaluation at UCI will be indicated by checking the appropriate lines. I will then put my initials next to the selected procedure if I agree to participate. Those procedures available to a pregnant woman are marked as "minimal risk to the fetus" all others are not available until after pregnancy has concluded. Those procedures which will be part of my billable care and those which will be conducted for free under a research protocol will be indicated in the table located later in this form.

Some of the samples which are required for this research might already have been collected for my diagnostic evaluations in other clinics. If these previous materials are adequate for the studies to be conducted, and it is my desire to make the materials available, then my previously collected biological materials and medical data might be used for this study.

Check /Initials

____ ____ Chart review: Data will be analyzed from my medical records. (Minimal risk to the fetus)

____ _____ Release of previously collected sample (i.e. blood, cell line, muscle etc.) (Minimal risk to the fetus)

____ ____ Physical Examination: Overall examination of my health will be done by Drs. June-Anne Gold, Moyra Smith, Taosheng Huang, Mike Zaragoza, Joseph Donnelly, Virginia Kimonis or Jay Gargus at the UCI Medical Center, the Gottschalk Plaza or the General Clinical Research Center (GCRC) located at the UCI campus (Takes 15-20 mins). (Minimal risk to the fetus)

____ ____ Photograph**:** Sometimes people with certain types of genetic disorders may look similar even though they are not related and photographs can help with diagnosis. Photographs of your face or body may be taken to be included in your research file. Photographs will not be altered in any way and the eyes will not be covered. Research files and photographs are stored in a secure location and can only be accessed by members of the research team.

____ ____ Blood Pressure: Painless application of blood pressure cuff. (Minimal risk to the fetus)

____ ____ Neuropsychiatric tests: A simple question and answer regimen to assess mental function (30 minutes). (not offered during pregnancy)

____ ____ Urine Metabolic Analysis: Collection of a one time sample or a 24 hour urine sample for analysis of body chemistry. (Minimal risk to the fetus)

____ ____ MRI scan: The painless use of magnetism and radio waves to produce detailed images of the tissues. After removing any metal objects on my body, such as jewelry or a wrist watch, I will lie on a table that slides into a tunnel-like MRI scanner. (The scan takes 30 to 60 minutes.) (not offered during pregnancy)

____ ____ CT scan: The painless use of X-rays and computer enhancement to obtain multiple cross-sectional images of my body creating an image of the organs. I will lie on a movable table that slides into the tunnel-like CT scanner. (The scan takes 30 to 60 minutes.) (not offered during pregnancy)

____ ____ Electrocardiogram: Test of heart function using application of electrodes to chest (Takes 10-15 mins). (not offered during pregnancy)

____ ____ Echocardiogram: The painless use of sound waves to measure heart function (Takes ~30 mins). (not offered during pregnancy)

____ ____ Echocardiogram with IV contrast: The painless use of sound waves to measure heart function. To enhance the echocardiogram images, a liquid that reflects sound waves ("contrast") is given through an IV (offered to adults only and not offered during pregnancy).

____ ____ Audiometry: A painless test of the ability to hear tones in ear phones (20 minutes). (not offered during pregnancy)

____ ____ Brainstem Auditory Evoked Response: A painless test of the brain's electrical response to audible clicks detected by electrode patches on my head (30 minutes). (not offered during pregnancy)

____ ____ Somatosensory Evoked Response: A painless test of response to tactile stimuli measured by electrode patches on the head (30 minutes). (not offered during pregnancy)

____ ____ Visual Field Examine: A painless test of the ability to perceive images on different regions of the retina (30 minutes). (not offered during pregnancy)

____ ____ Visual Evoked Response: A painless test of the ability to perceive light patterns and light flashes as detected by electrode patches on the head (30 minutes). (not offered during pregnancy)

____ ____ Electroretinogram: A harmless procedure involving placing contact lenses attached to wires on your eyes and assessing the retinal response to flashing lights (30 minutes).

____ ____ Collection of Hair: A few hairs with the hair root will be plucked from my body to be used for DNA tests (Takes less than 5 mins). (Minimal risk to the fetus)

____ ____ Collection of Buccal Cells: The specialist will wipe the inside of my cheek with a cotton swab to collect cells which will be used for DNA testing (Takes less than 5 mins). (Minimal risk to the fetus)

____ ____ Collection of Urine Cells: Collection of a urine sample, and recovering the suspended cells for DNA tests (Takes less than 5-10 mins). (Minimal risk to the fetus)

____ ____ Collection of a Venous Blood Sample: My blood will be collected, up to two times, by inserting a needle into a vein in my arm. If I am an adult, I will give up to 12 teaspoons (60ml) of blood. If I am minor I will give an amount of blood proportional to my age: If I am between 14 and 17 years of age, I will give up to 8 teaspoons (40ml) of blood ; If I am between 6 and 13 years, I will give up to 5 teaspoons (25ml) of blood; If I am between 2 and 5 years, I will give up to 4 teaspoons (20ml) of blood; and if I am less than 2 years, I will give up to 2 teaspoon (10 ml) of blood. My blood will be taken at phlebotomy center such as at the UCI Gottschalk Medical Plaza by qualified personnel. My blood will be used for standard blood chemistry, as well as to perform DNA and other molecular tests, and to establish cell lines for continued genetic, metabolic, and molecular studies. (Takes about 5-15 mins) (Minimal risk to the fetus)

____ ____ Skin biopsy A sample of my skin will be collected, one time only, by Drs. Taosheng Huang, Mike Zaragoza, June-Ann Gold, Virginia Kimonis, Joseph Donnelly or Jay Gargus at the UCI Medical Center, the UCI Gottschalk Plaza, the General Clinical Research Center (GCRC) located at the UCI campus, or another offsite location (Takes 15-20 mins). A two square inch area on my arm will be cleaned with rubbing alcohol. This area will then be numbed with Lidocaine. With a scalpel punch we will then quickly obtain a skin sample of less than one quarter of a square inch. The area will then be closed with a bandage. This is done to develop a fibroblast cell line, which will allow the study of mitochondrial metabolism, and molecular changes. (not offered during pregnancy)

____ ____ Muscle Biopsy: A sample of my muscle will be collected, one time only, by Dr. Swaraj Bose, MD at the UCI Medical Center or other approved UCI surgery site at once from my thigh or arm to assess muscle structure, body metabolism, and molecular changes. The muscle biopsy will vary in size depending on the tests to be performed and my age. If I am and adult, will be asked to provide no more than 4 grams of muscle. The area of sample collection will be anesthetized with Lidocaine HCL, 1:200,000 epinephrine, a small incision made in the skin, a sample of muscle removed, and the incision will be sutured. The sutures will not need to be removed, but will dissolve in about two weeks. The surgery will take about an hour. Generally, this procedure will be conducted as an outpatient. However, under certain circumstances the physician may decide that it would be beneficial to me to be kept in the hospital over night. If I am a minor the amount of tissue to be taken and the anesthetic to be used will depend on my age, size and health status based on the recommendations of the doctors. In general, if I m between 16 and 17 years of age, the sample will not exceed 4 grams and will be collected under local anesthetic; if I am 10 to 15 years old, the muscle sample may be up to 2.5 grams and the anesthetic might be either local or general; if I am 3-10 years the sample could be up to 2 grams and collected under general anesthetic; and if I am under 3 years old the sample could be up to 1 gram, collected under general anesthetic. If my muscle is collected under general anesthetic, I will generally be kept in the hospital overnight for observation. If I am a minor, but the muscle is collected using a local anesthetic, then I might be asked to stay over night in the hospital or I might be permitted to go home after the biopsy, depending on the recommendation of the doctors. My tissue will be used for DNA and other molecular tests and histological examination. (not offered during pregnancy)

____ ____ Diffuse Optical Spectroscopy (DOS): The DOS measurement consists of placing a probe onto the surface of my body (calf, bicep, or head). This probe will be secured by either gentle hand pressure or fastened to my skin using clinically-approved wraps such as Corbin/wrap bandages or medical adhesive tape and medical glues. Several dots will be made on my skin outlining the probe with a surgical felt tip marker. This is so we would be able to put the probe again on the same spot in case that we needed to interrupt the measurement. The probe looks like a bar code scanner in a supermarket and it shines infrared light on my skin. There is no radiation involved with this light. In some cases where light signals are low, the optical detector will be placed directly onto my skin (but contained within an electronically shielded casing, and placed inside another plastic casing). (not offered during pregnancy)
Following the baseline DOS measurements, I will perform a strength test and then perform a bout of exercise. I will also have a heatpad and a coldpad applied to my arm at different timepoints. DOS measurements will be taken both before and after the exercise, temperature and glucose tolerance challenge. The exercise challenges will be as follows:

Bicep: Following the baseline DOS measurements, I will be asked to perform a strength test to determine the load that is appropriate for me for the subsequent exercise. I will then be asked to perform a bout of exercise using my nondominant arm. The exercises will consist of:
(a) isometric contractions: Isometric contractions will be performed using custom or commercial dynamometers that measure grip strength, or therapeutic putties (i.e., Eggercizer) used by physical therapists. I will be asked to grip the Eggercizer as hard as I can and hold it for as long as I can. This exercise will be repeated 3-5 times.
(b) repeated sets of biceps exercise (arm "curls" - extension and flexion of the elbow joint). I will be asked to perform arm curls with a weight that is only 70% of the maximum weight that I was able to use in the strength test. Each set will consist of 15-20 repetitions. I will be asked to perform a minimum of one and a maximum of three sets depending on how I feel. The exercise will be performed with either dumbbells or an exercise machine specifically designed for this purpose (Biodex). Following this exercise bout, DOS will be repeated. Comparisons of DOS-measured hemoglobins and cytochrome redox state will be made between the exercised and non-exercised arm.

(2) Calf: Following the baseline DOS measurements, I will be asked to perform single leg heel raises. The study team will ask me to stand, hold something for balance, and remove one foot off of the ground that will not be exercised. I will then be asked to lift the heel of the foot resting on the ground over and over until fatigue (Essentially I will be standing on one foot and going up and down on my tiptoes with the other foot). Following this exercise bout, DOS will be repeated. Comparisons of DOS-measured hemoglobins and cytochrome redox state will be made between the exercised and non-exercised calf.

Total measurement time will be less than 30 minutes. Some additional procedures may include:

(1) Pulse oximetry (to determine heart rate and SaO2 level)
(2) Skin fold caliper (to determine fat layer thickness)
(3) Ultrasound (to determine fat layer thickness)
(4) Measurement of leg/arm diameter using measuring tape

(3) Blood Pressure Cuff Test: I will be asked to lay still while a blood pressure cuff is put on my arm. After 5 minutes of rest, the cuff will be inflated and the pressure will be kept on my arm for 3 minutes. The cuff will then be instantly released and I will rest for 5 more minutes. This cycle may be performed a total of three times, depending on how I feel, and DOS measurements will be taken throughout.
If I am interested, and if instrument availability allows, I may be asked back for repeat DOS measurements on another day. Repeat DOS measurements will be the same as my initial DOS measurement session, including the additional procedures listed above. (not offered during pregnancy)

____ ____ Micro-organic Breath Analysis: I may be asked to submit several breath samples. This requires that I will breathe into a stainless steel canister. I may have to do this up to 5 times and I may be required to hold my breath for several seconds. This is done to see whether certain metabolites in my body can be measured without taking blood or tissue and may avoid invasive procedures in the future. These measurements may be taken at various times during a 60 minute period. (not offered during pregnancy)

____ ____ Lumbar Puncture: Lumbar Puncture will be taken, one time only, by Pat Tully, NP of the UCI Medical Center or other approved UCI surgery site. After numbing the region with cold and/or a local anesthetic (Lidocaine), a small needle will be inserted in the lower back below the spinal cord and a small sample of cerebral spinal fluid (CSF) will be collected. If I am an adult, up to 1 teaspoon (5 cc) of CSF might be collected, generally in conjunction with a Lidocaine local anesthetic. However, if I am a minor, then proportionately less CSF will collected depending on my age, size and health. If I am 16 to 17 years, up to 1 teaspoon (5 cc) might be collected, if I am 10-15 years then up to ½ teaspoon (2.5 cc) might be obtained; if I am 3-10 years than up to ¼ teaspoon (1.25 cc) might be collected; and if I am under 3 years old then up to 1/8 of a teaspoon (0.5 cc) might be collected. These collections will be conducted following chilling the area for needle insertion and if appropriate local anesthetic. The precise amount of CSF collected and the anesthetic used will be decided by the doctors based on what is best for my wellbeing. The spinal fluid will be used to help my diagnosis as brain chemistry and possibly cells. After the procedure, I have to lay flat for about one or two hours. (not offered during pregnancy)

____ ___ Mitochondrial diseases are complex, multi-system disorders of often unknown origin. Many genetic defects previously described may not yet have been linked as the underlying cause of mitochondrial disease. Also many genetic defects causing mitochondrial disease have not yet been discovered. Often laboratories other than the MITOMED group are involved with the investigation of such genetic defects and they are experts in their field. By initialing on the line I agree that the MITOMED laboratory may share my biological sample with such expert groups. However, my name and other identifying information will not be disclosed to anybody outside of the MITOMED group. No costs will incur due to any of such research testing to me or my insurer. (Minimal risk to the fetus)

____ ____ I do not wish to receive any results generated from this study. Participation is solely to advance knowledge of mitochondrial disease. My insurance carrier will not be charged for any tests and results will be kept confidential within the study team and will not be released to my health care provider. (minimal risk to fetus)

____ ____ I choose to know results that researchers may discover on my biological sample (not eligible for fetal samples). Only results from CLIA (Clinical Laboratory Improvement Act) approved tests may be released to me. Experimental data generated under research protocols which have not yet reached CLIA approval may not be released to me by law. Genetic information may affect my future ability to get health and life insurance and ability to get a job or cause emotional discomfort. (not offered during pregnancy)

I can withdraw from this study at any time without any obligations or consequences. I might be terminated from further study if it becomes clear that I do not have a mitochondrial problem, and/or financial, facility and/or personnel resources become inadequate to continue the studies.

RISKS:

The possible risks and/or discomforts associated with the procedures described in this study are minimal or/and moderate. Of these procedures pregnant women only may participate in blood draw. The procedural risks are as follows:

Minimal risk for collection of a venous blood sample: At the time of collection, there will be some discomfort from the needle insertion, and there is some possibility of bruising, swelling, bleeding, and infection at the site of the needle insertion, also rarely of fainting. (No additional risk to the fetus)

Minimal risk for collection of a skin sample: At the time of collection, there will be some discomfort from the scalpel punch insertion, and there is some possibility of bruising, swelling, bleeding, and infection at the site of the scalpel punch insertion, also rarely of fainting

Moderate risk for echocardiogram with IV contrast: An echocardiogram is considered safe, because the test uses only sound waves to evaluate your heart. These high-frequency sound waves have not been shown to have any harmful effects. According to recent studies, the contrast liquid is not associated with significant side effects. There is a chance of an allergic reaction to the contrast liquid, which is itching that is relieved by Benadryl. There is also a chance of nausea, back pain, and flushing which pass within minutes. There will be some discomfort from inserting the IV in order to give the contrast liquid, and there is some possibility of bruising, swelling, bleeding, and local infection at the site of the needle insertion, also rarely of fainting. Risks will be minimized by using new, sterile equipment and by limiting the time that the IV is in place. Experienced staff will be used and a physician will supervise the procedure.

Minimal risk for MRI scans: MRI examinations release radio waves, which are very noisy. Although radio and magnetic waves used in MRI examinations are not associated with any known side effects, long term effects still remain undetermined. I may experience brief claustrophobia (fear as a result of being in a small, enclosed space) during the MRI procedure. If this happens, I may request to end my participation in the MRI procedure.

Minimal risk for CT scans: The use of a CT scan has a small increase risk of cancer in the future.

Moderate risk with muscle biopsy: There is the potential for pain, bleeding, and infection at the site of the incision. A scar will remain after the incision has healed. While the incision site will be sore and may limit movement for several days, there will not be any permanent muscle weakness. If I need to have general anesthesia I could have a bad reaction to the medication, a sore throat, a seizure or heart attack. My thinking may be unclear for awhile after the procedure, also in rare cases my temperature may go up very high. As with all general anesthesia there is a small risk of death. I will be seen before the muscle biopsy by the surgeon and the anesthetist to consider the potential risks and benefits of this muscle biopsy and special recommendations and medical evaluations will be made.

Minimal risk with DOS: Standard clinical wraps may be used to fasten probes to the skin and may cause irritation. I may experience some muscle soreness in my calf or bicep after the exercise challenge. If I feel I cannot complete the exercise challenge I will not be asked to perform the challenge. If I show signs of fatigue during the exercise challenge I will be allowed to stop. I may feel some discomfort after inflation of the blood pressure cuff and there is some possibility of bruising or skin discoloration. If I feel that the pressure is too uncomfortable, I can ask the researchers to stop and they will immediately release the pressure.

Moderate risk with spinal tap: Lumbar puncture generally produces little discomfort, though severe headaches sometimes occur. Infections and bleeding are rare, and nerve injury has rarely been observed. Decreased blood pressure and leaking of cerebral spinal fluid are other rare risks associated with lumbar puncture. A pain reliever and antibiotics will be prescribed by the doctor for the adverse effect explained above. The medical staff will be available to address any further problems.

Breach of Confidentiality: There is a possible risk of breach of confidentiality since personal information including family history will be obtained, although all efforts will be made to minimize this.

If I choose to know the results that the researchers obtain on my biological sample, the risk of discrimination due to genetic testing has recently been reduced: The passage of the Genetic Information Nondiscrimination Act (GINA) of 2008 provides legal protection against insurance and employment discrimination. However, this law has currently not been tested in court, so it is possible that genetic information may affect my or other family members future ability to get health and life insurance and ability to get a job. This information might also cause emotional discomfort. For example, it might reveal unexpected information about family relationships such as non-paternity or adoption or the information gained may also allow risk assessments for other family members for the same genetic disorder. It is up to me to share the results from this study with those members of my family. There may also be risks to participation that are currently unforeseeable.

BENEFITS:

I may not benefit directly other than possibly obtaining accurate diagnosis of my condition. However, this study may help researchers understand more about mitochondrial diseases, including diagnosis and treatment. The research conducted with the specimens and cell lines that I donate is likely to require years of study, and is not guaranteed to yield positive results.

ALTERNATIVE TREATMENTS:

This study is not being performed to improve my health or well-being. I have the option of not participating to this study.

COST/COMPENSATION:

It will not cost me anything to be in this study and I will not be paid for participation. There is no compensation for travel. Study-related long-distance phone calls will be handled as follows: When I am placing a call to the study team from out of the area the study team will call me back as to not incur any charges for long distance calls.

If I am injured as a result of my participation in this study, I will be provided reasonable and necessary medical care to treat the injury at no cost to me or to my insurer/third party payer. The University of California does not routinely provide any other form of compensation for injury. I must report any suspected study-related injury to the study investigator immediately.

Cost will not be billed to me or my insurer for studies that are not checked in the table below, classified under billable standard care.

	Billable standard care		Research	
	Check (√)	**Initial**	**Check (√)**	**Initial**
Clinical Evaluations				
General Physical Examination				
Neurological Evaluations				
Ophthalmological Evaluations				
Gastrointestinal Evaluations				
Audiometric Evaluations				
Cardiology Evaluations				
Genetic Evaluations				
Genetic Counselings				
Other Clinical Evaluations:				
Possible Hospitalizations				
Sample Collections/ Procedures	**Billable standard care**		**Research**	
	Check (√)	**Initial**	**Check (√)**	**Initial**
Hair Collections				
Urine Collections				
Buccal Swab or Saliva Collection				
Blood Collections				
Skin Biopsy				
CSF Collection, Lumbar Punctures				
Muscle Biopsy				
Imaging	**Billable standard care**		**Research**	
	Check (√)	**Initial**	**Check (√)**	**Initial**
Audiometry				
Visual Field Exams				
Visual Evoked Responses				
Electroencephalography (EEG)				
Brainstem Auditory Evoked Responses				
Somatosensory Evoked Responses				
Electromyograms (EMG)				
Electrocardiograms (EKG)				
Echocardiograms				
Echocardiograms with IV contrast				
MRIs				
CT Scans				
Laboratory Analyses	**Billable standard care**		**Research**	
	Check (√)	**Initial**	**Check (√)**	**Initial**
Cell Line Preparation				

Mitochondrial Isolation				
Histochemical Anaysis				
Light Microscopic Evaluation				
Electron Microscopic Evaluation				
Mitochondrial Biochemical Analyses (Electron transport chain studies) (Respiration Studies)				
Other Biochemical Evaluations (i.e PDC studies)				
Blood, Urine or CSF Metabolic Analyses: i.e. Lactate, Pyruvate, Organic Acid screen, Aminoacid screen, Carnitine Profile etc				
Molecular Mitochondrial Tests:	**Billable standard care**		**Research**	
	Check (√)	**Initial**	**Check (√)**	**Initial**
MtDNA Rearrangement Analyses				
MtDNA Base Substitution Analyses:				
MtDNA Sequence Analyses:				
nDNA Mitochondrial Gene Analyses:				
Confirmatory CLIA Approved Laboratory Studies of research results: (not approved for fetal samples)				
Other DNA Tests (SCAs, SMA, etc)				
Linkage Analysis				
Cytogenetic analysis				
Research Only	**Research**			
	Check (√)	**Initial**		
Mitochip analysis				
Diffuse Optical Spectroscopy (DOS)				
Micro-organic Breath Analysis (MOBA)				

CONFIDENTIALITY:

My research records will be stored in a very restricted-access area. Identifiable research data (including names, medical records, and photographs) will be stored in a secure, locked location and electronic data will be stored on a secure, password-protected computer network. The research team, authorized UCI personnel, the study sponsor, and regulatory entities may have access to my study records to protect my safety and welfare. Any information derived from this research project that personally identifies me will not be voluntarily released or disclosed by these entities without my separate consent, except as specifically required by law.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

OTHER CONSIDERATIONS:

Any specimen(s) (e.g., tissue, blood, urine) obtained for the purposes of this study will become the property of the University of California, Irvine (UCI). Once you provide the specimens you will not have access to them if your name can no longer be linked to the sample. Otherwise you can withdraw a specimen at anytime. The specimens will be used for research and such use may result in inventions or discoveries that could become the basis for new products or diagnostic or therapeutic agents. In some instances, these inventions and discoveries may be of potential commercial value and may be patented and licensed by the University. You will not receive any money or other benefits derived from any commercial or other products that may be developed from use of the specimens. The specimens may also be shared with other researchers who are not a part of this study; however, no identifiable information (e.g., name, medical record number) will be released to anybody outside of the MITOMED group.

The study team has no disclosable financial interest in the outcome of this study.

NEW FINDINGS:

If, during the course of this study, significant new information becomes available that may relate to my willingness to continue to participate, this information can be provided to me by the investigator. The information will only be provided if I have indicated my wish to know the results of the study and initialed above.

CLIA (Clinical Laboratory Improvement Amendments 1988) regulations prohibit release of laboratory records unless they have been previously certified by a CLIA approved laboratory. Results for a number of biochemical or molecular defects can be confirmed by a reference laboratory like the ORPHAN disease laboratory at UCLA or the Center for Inherited Disorders of Energy Metabolism at Case Western University. The cost for this confirmation varies on the type of test but is approximately $350.00 – $500.00 per sample and can be billed to my insurance carrier at my request. If my insurance carrier can not be billed and personal funds are not available it may be possible to have the cost of confirmatory testing billed to the grant, funding this research project at the discretion of the Principal Investigator.

Information from this research may have some meaning for my future health. This information, including genetic information, will be made available at my request as outlined above. Sometimes genetic information may affect my future ability to get health or life insurance and my ability to get a job. Sometime genetic information will cause emotional discomfort and also may reveal potential nonpaternity or adoption. The information gained may also allow risk assessments for other members of my family for the same genetic disorder. It is up to me to share the results from this study with those members of my family. A genetic counseling session will be offered to me free of charge to minimize the emotional burden. I can also discuss paternity/maternity issues with the genetic counselor ahead of genetic testing should this be an issue. It will be up to me if I want to share this information with my doctor and have it in my medical record. I will be provided with a copy of the brochure "Genetic Information, Privacy & Discrimination" published by the National Society of Genetic Counselors to provide further information regarding this issue.

IF I HAVE QUESTIONS:

If I have any comments or questions regarding the conduct of this research or my rights as a research subject, I will contact the Office of Research Administration by phone, (949) 824-6068 or (949) 824-2125, or at 300 University Tower, Irvine, CA 92697-7600.

VOLUNTARY PARTICIPATION:

I have read the attached "Experimental Subject's Bill of Rights" and have been given a copy of it and this consent form to keep. Participation in this study is voluntary. I may refuse to answer any question or discontinue my involvement at any time without penalty or loss of benefits to which I might otherwise be entitled.

My decision will not affect my future relationship with UCI or quality of care at UCI Medical Center. My signature below indicates that I have read the information in this consent form and have had a chance to ask any questions I have about the study. I consent to participate.

Signature of Subject (ages 16 and older)	DATE
Printed Name of Subject	DATE
Signature of Parent/Legally Authorized Representative	DATE
Printed Name of Parent/Legally Authorized Representative	DATE
Signature of Parent/Legally Authorized Representative	DATE
Printed Name of Parent/Legally Authorized Representative	DATE
Signature of Witness	DATE
Printed Name of Witness	DATE
Signature of Investigator	DATE
Printed Name of Investigator	DATE

UNIVERSITY OF CALIFORNIA, IRVINE
Experimental Subject's Bill of Rights

The rights listed below are the right of every individual asked to participate in a research study. You have the right:

1. To be told about the nature and purpose of the study.

2. To be told about the procedures to be followed in the research study, and whether any of the drugs, devices, or procedures is different from what would be used in standard practice.

3. To receive a description of any side effects, discomforts, or risks that you can reasonably expect to occur during the study.

4. To be told of any benefits that you may reasonably expect from the participation in the study, if applicable.

5. To receive a description of any alternative procedures, drugs, or devices that might be helpful, and their risks and benefits compared to the proposed procedures, drugs or devices.

6. To be told of what sort of medical treatment, if any, will be available if any complications should arise.

7. To be given a chance to ask any questions concerning the research study both before agreeing to participate and at any time during the course of the study.

8. To refuse to participate in the research study. Participation is voluntary. You may refuse to answer any question or discontinue your involvement at any time without penalty or loss of benefits to which you might otherwise be entitled. Your decision will not affect your right to receive the care you would receive if you were not in the experiment.

9. To receive a copy of the signed and dated written consent form and a copy of this form.

10. To be given the opportunity to freely decide whether or not to consent to the research study without any force, coercion, or undue influence.

If you have any concerns or questions regarding the research study you should contact the research team listed at the top of the consent form.

If you are unable to reach a member of the research team and have general questions, or you have concerns or complaints about the research study, research team, or questions about your rights as a research subject, please contact the UCI's Human Research Protections Program in the Office of Research Administration by calling (949) 824-6068 or (949) 824-2125 Monday – Friday, 8 am – 5 pm; or by e-mail at IRB@rgs.uci.edu; or by writing us at University Tower - 4199 Campus Drive, Suite 300, Irvine, CA 92697-7600.