MUSCLE BIOPSY

for mitochondrial and metabolic disorders

FREQUENTLY ASKED QUESTIONS

Note: The information contained in this document is not intended nor should it replace a one on one discussion about your specific issues with a healthcare provider. It is not meant to be a substitute for professional one on one advice by qualified doctors, allied medical personnel, and other professional services. The responsibility for any use of this information rests with you.

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Most up to date version may be found at:

www.virtualmdpractice.com/musclebiopsy.html

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INTRODUCTION BY FRAN KENDALL, M.D.

A muscle biopsy is an invasive and costly procedure. Requiring a muscle biopsy for you/your child to determine if a mitochondrial or other metabolic muscle disease is a cause for you/your child's problems can be a hectic, frustrating, and stressful time often without a sense of control. We wish to change that.

We believe that information empowers patients and it is our hope that this document will encourage you to ask questions of your health care providers so you can determine if a biopsy or the approach to a biopsy is appropriate to your situation, what you can typically expect from a biopsy, its utility to your unique situation, and what to be mindful of during this process.

A bit of good news is that the field of mitochondrial medicine is rapidly changing and new innovative testing currently under development may make biopsies obsolete. This new DNA based testing may be available within the next 12 months, or less. We will watch the development of this testing closely and will be happy to provide updates if contacted directly.

We are strictly a clinical practice with no laboratory affiliation or financial/research incentive in the tests we order. The following information is strictly the opinion of Virtual Medical Practice, LLC and is not meant to be the single resource for information about muscle biopsies for mitochondrial and metabolic disorders. This document is a compilation of ideas and thoughts from a number of resources including patients, guardians, and patient advocacy groups.

We are grateful for the input and suggestions of all those who freely gave of their time and effort. I also wish to acknowledge the courage and grace that my patients exhibit and how they are an inspiration to us. I hope this document in some small way reaches out to those that need that courage and grace the most.

Sincerely,

Fran Kendall, M.D.
Medical Genetics, CEO

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WHY A MUSCLE BIOPSY?

Although more and more forms of mitochondrial disease can now be detected by simple blood tests which avoid the need to have a biopsy (see additional information in this document and always ask your health care provider if you may be such a case), a number of patients still may require a close look at their energy producing pathways in the muscle. Special studies on muscle tissue have long been the standard for investigating most cases of mitochondrial or other metabolic myopathies.

Mitochondrial diseases affect the body's ability to efficiently convert the food we eat into energy packets, known as ATP. This final conversion occurs within a series of chemical reactions that take place in the five complexes of the electron transport chain. The electron transport chain is also known as the respiratory chain and the process whereby energy is created using oxygen and phosphorus is called OXIDATIVE PHOSPHORYLATION.

A tissue rich in mitochondria is needed to look closely at the energy producing pathways. The tissues in the body that house the most mitochondria are the brain, kidney, liver, heart, and skeletal muscle. As most of us would object to donating a part of our liver or kidney for testing, it becomes quite clear why muscle tissue is chosen for mitochondrial studies! In other metabolic myopathies (metabolic muscle disease), muscle tissue is selected to investigate since that is the organ that is most affected. The mitochondria are removed from the muscle tissue and studied using special instruments such as a spectrophotometer. By using these special instruments in the laboratory the interpreting physician is able to tell whether or not a specific person makes energy as well as normally expected.

IN BROAD TERMS, WHAT ARE THE STEPS WITH A BIOPSY?

It may be helpful to understand the process as there are many paths and many physician approaches that can bring you to the point of a biopsy. The following is not a generic biopsy process but an example of the series of steps that typically occur when a geneticist is involved:

- Typically a patient will come to a geneticist who specializes in mitochondrial/metabolic disorders one of three ways:
  - a referral from their primary physician,
  - a referral from their neurologist,
  - or a patient will locate and contact a geneticist directly.
- Some insurance companies may require that a patient has a referral from their primary physician or neurologist prior to meeting with a geneticist.
- It is standard practice that the geneticist meets with the patient and reviews their records and any testing done to date prior to recommending or scheduling a biopsy. This is to

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determine if the patient should have a biopsy or whether there are any other tests or procedures that can be performed that may rule out the need for a biopsy.

- If a muscle biopsy is warranted, the geneticist will coordinate the biopsy with the surgeons and labs involved.
- Typically the surgeon and the labs will work with you and your insurance directly regarding insurance coverage approval.
- The labs will report their findings directly to the geneticist.
- The geneticist will interpret and/or compile the various results into a report that should be easily understood by either the patient/guardian or at least by the patient's primary physician.
- The report will be shared with the patient/guardian and those physicians that the patient/guardian has requested to receive a copy.
- Most geneticists will contact you directly with the results, especially if the results are abnormal. Lab personnel, office staff, or even a General Pediatrician or primary provider may not be comfortable having a discussion with the patient/guardian regarding the results. As a result, it is helpful to understand the availability of the geneticist to discuss the information in depth.

ARE THERE ANY OTHER LESS INVASIVE AND LESS COSTLY TESTS THAT CAN BE PERFORMED THAT MAY RULE OUT THE NEED FOR A BIOPSY?

Yes, in some cases. It is in rare cases that a biopsy is the first course of action and is typically only suggested after the patient is seen by a physician that is also a trained geneticist or a neurologist with metabolic experience. Regardless, if a referring physician requests a biopsy be performed, a geneticist or neurologist with metabolic experience typically should first see the patient to determine if a biopsy is truly warranted. Completing some tests FIRST may circumvent the need for an invasive and costly procedure. A chromosome microarray study may be warranted if the adult or child has other neurological issues including long standing development or learning problems, seizures, etc. In addition and depending on clinical symptoms, a simple blood draw for DNA testing can be done and the results may negate the need for a biopsy.

For example, a chromosome microarray study from a simple blood draw scans the entire genetic blueprint of the person at a high level for deletions or duplications (missing or extra pieces of genetic material). Any found deletions or duplications may be the cause of the problems, and having this knowledge could rule out the need for muscle testing.

Even if a muscle biopsy is required, when analyzing the tissue there may be some tests that can be performed in a stepwise approach that can drastically reduce costs. Essentially, perform test A before test B, since if test A determines there is an abnormality, there may be no pressing reason to perform and incur the cost for test B. It may be wise for you to

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determine if this stepwise approach will be applied by the provider that you are considering for completion of the biopsy.

The previous example simply illustrates that biopsies are not the end all for ALL patients. In recent months, we have re-diagnosed patients with other disorders who were previously believed to have primary mitochondrial disease based upon muscle biopsies. Due to certain clinical symptoms and information in their medical records, a simple blood test for a chromosome microarray study determined that several of these patients have a chromosome issue rather than a mitochondrial disorder. This re-diagnosis significantly alters treatment protocols and inheritance risks for related family members.

WHAT ARE THE FACTS ABOUT FRESH VS. FROZEN MUSCLE BIOPSIES?

This is a topic often debated when discussing muscle biopsies. Although some studies completed a number of years ago showed that freezing can affect the integrity of complex I, advancements in the collection and processing protocols of the muscle sample currently avoid or minimize these differences.

Complex 1 is the first and most commonly affected component (part) of the energy producing pathway resulting in mitochondrial disease. Data from a previously owned biotech firm comparing fresh vs. frozen samples showed that while complex I activity was at times more robust in fresh samples, the end results were otherwise comparable, indicating that the frozen samples were just as likely to diagnose a patient with a mitochondrial disorder as a fresh biopsy when a biochemical defect was truly present in the patient. The risk benefit ratio of a fresh vs. frozen sample should be seriously measured when making the decision for you or your family member given the extravagant costs, related travel expenses, loss of work income, etc. to visit one of only a few centers that provide fresh biopsies in comparison to a frozen biopsy.

It is important to know that at some centers, such as the Cleveland Clinic, additional testing on fresh muscle has been suggested to detect diagnostic abnormalities in up to 20% of those who would have otherwise gone undiagnosed had they been evaluated with frozen tissue studies only. However, it is also important to understand that not all labs doing fresh samples are equal. Specifically, some labs use of “additional testing” data, specifically respirometry, for diagnosis is very concerning among mitochondrial experts and felt to be inaccurate.

In most cases, parents, patients and family members can feel confident that a frozen muscle biopsy, especially when performed in conjunction with a thorough clinical evaluation by a trained geneticist or metabolic specialist, will be as accurate as a fresh biopsy in providing a mitochondrial disease diagnosis.

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WHAT INFORMATION IS CONTAINED IN OR MAY I EXPECT FROM A MUSCLE BIOPSY REPORT?

It is reasonable to expect that the report with your muscle biopsy results should be understandable to you and your primary care physician. It should clearly state if the patient does or does not have a mitochondrial or other metabolic myopathy as a cause for the symptoms in question. Ask the provider to provide a sample report.

The muscle obtained at the time of biopsy is typically used for histological/ histochemical studies and enzymology. The histology studies look at the general structure of the muscle tissue and for the presence or absence of various compounds and chemicals that provide clues to the "health" and function of your/your child's muscle tissue. These findings can be very helpful if they confirm abnormal DNA or enzyme testing, but be aware that these studies can report out as normal even in patients who are ultimately proven to have a mitochondrial disease or other metabolic myopathy. In essence, these studies provide solid evidence/support or another layer of confidence that you or your family member indeed have the disorder in question.

Some laboratories use control mechanisms to assure that the results you receive are valid and accurate. Feel free to ask if these controls will be used during the analysis of your biopsy.

HOW WILL A BIOPSY HELP ME?

Deciding to pursue a muscle biopsy when faced with the possible diagnosis of a mitochondrial disorder is a very difficult decision for many patients and families. A biopsy can help to better confirm or rule out a diagnosis, depending upon the accuracy of the testing and processing laboratory. Having a diagnosis means that you and your physicians will know the cause of your underlying disease, and how to treat it even if that treatment is limited and/or restricted to symptomatic therapies, as is usually the case for many mitochondrial disorders. Having a diagnosis when experiencing any further symptoms will arm other physicians, such as those in the ER, with the knowledge of what to be careful of, what to look for, and how to quickly treat or stabilize a patient. It also provides the understanding of what this means for individuals over time (i.e. prognosis) as well as the impact it may have on additional children or other family members. In addition, having a diagnosis enables the diagnosed individual to enter into research or clinical treatment trials for a given disease that are not available to undiagnosed patients. If a biopsy rules out mitochondrial disease, then actions can be taken to focus on other areas that may be causing you or your family member's issues.

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WHAT IS THE COST OF A MUSCLE BIOPSY?

Muscle biopsies are expensive. Frozen biopsies are far less expensive than fresh biopsies and depending on the center and the testing that is included as a part of the biopsy package, costs can range from several thousand to tens of thousands of dollars. Be aware that the price tag for this procedure includes surgical and anesthetic costs as well as the actual testing fees. Although much of it may be covered by your insurance, typically there are out of pocket expenses regardless of your coverage and a biopsy can become expensive quickly. Be aware that:

PRE-APPROVED DOES NOT MEAN YOU ARE NOT FINANCIALLY RESPONSIBLE

You may become financially responsible for a significant portion even though your insurance "pre-approved" the biopsy. Carefully review the forms that any providers ask you sign. Ask as many questions as you need to become clear on what your responsibilities are and what the provider's responsibilities are. The best centers will be forthright with their answers and will honor your questions.

FACTORS THAT CAN IMPACT WHAT YOU MAY BE RESPONSIBLE FOR

There are many factors that can impact what you are financially responsible for and the following are just a few of the more common variable factors:

- Whether the lab is under contract with your insurance.
- If there will be any add-on testing that the lab or provider orders AFTER the biopsy has been pre-approved with your insurance. In some cases you are unaware of these add-on tests until it is too late.
- Any testing or procedures that are not covered but billed for by the provider.
- Insurance filing mishaps caused by either the insurance company or the provider in which the insurance company will not pay the provider, and for which you then become financially responsible due to an agreement you may have signed.

LIFETIME INSURANCE CAPS

Even if your insurance company covers the cost of a biopsy, there are lifetime caps on insurance expenditures that add up over the years. Spending tens of thousands of dollars on a biopsy when there may be other less expensive options may need to be carefully considered, especially if there are limitations on one's allotted health care dollars.

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WHAT ARE MY OPTIONS TO REDUCE THE COST OF A MUSCLE BIOPSY?

One of the simplest ways to reduce costs is to have only the testing you or your family member requires to help diagnose your case. In most cases you can insist testing be done in a stepwise fashion on frozen samples unless there is a compelling reason to do otherwise.

For example:

Step 1) Histological and histochemical muscle studies should be completed on collected tissue as the first step. These studies look at the general structure of the muscle tissue and for the presence or absence of various compounds and chemicals that provide clues to the "health" and function of your/your child's muscle tissue.

Step 2) Review the histology results provided by the lab with your primary physician before moving forward with any additional testing. Keep in mind, however, that histological studies that return normal do not mean you/your child don't have a mitochondrial or other metabolic myopathy. If this testing shows disease specific changes then it can provide information to a more cost-effective approach for your continued work-up.

Step 3) Next, mitochondrial enzymology should be completed or other enzyme testing if another metabolic myopathy is considered.

Step 4) Review the enzymology results provided by the lab with your primary physician before moving forward with additional DNA testing.

Sometimes there may be a compelling reason to complete a fresh muscle biopsy which typically includes histology, enzymology, as well as other studies such as respirometry. However, and as is the case with frozen samples, you can still review these results with your primary provider prior to authorizing any additional DNA testing such as mitochondrial Southern blot analysis, various point mutations, or depletion studies. While these additional DNA tests may be useful in CERTAIN cases, they are clearly not indicated in ALL patients. They can be added AFTER the results of the histology and enzymology are known.

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DOES THE PROVIDER ORDERING THE TESTING HAVE ANY CONFLICT OF INTEREST?

Some physicians do have an interest in the testing that they order as they may have:

- Ownership, stock, or a financial interest in surgical centers, hospitals or laboratories they plan on using,
- receive financial incentives from pharmaceutical or biotech companies,
- have research grants,
- have other arrangements that are linked to your care.

Most physicians will remain open and honest about these conflicts of interest and will always have your best welfare and care in mind, as medical ethics dictates they avoid ordering excessive or un-necessary testing or procedures, intentionally driving up their research data, or hording tissue samples.

Requesting a full disclosure on conflicts of interest simply is good practice. At Virtual Medical Practice, we have no laboratory affiliation or financial/research incentives in the tests we order.

WHAT ABOUT AFTER THE BIOPSY?

There are a number of issues to be aware of after the biopsy is performed that are covered in the following Questions to Ask Your Provider section of this document. They cover:

- if any genetic material remains after the biopsy
- rights to your genetic material,
- storage and security of your genetic material,
- releasing your genetic material
- research that may or may not be performed on your genetic material.

We suggest you become familiar with these issues before contacting or signing any provider forms.

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IMPORTANT QUESTIONS TO ASK YOUR PROVIDER WHEN CONSIDERING A MUSCLE BIOPSY

Before proceeding with an expensive, invasive test, the following are a few of the questions that your provider should be more than willing to address and answer before the biopsy proceeds.

WHY IS A BIOPSY RECOMMENDED?

The answer should be clear, reasonable, and understandable to you.

WHY NOT PERFORM LESS COSTLY AND LESS INVASIVE TESTS FIRST AND THEN PROCEED WITH A BIOPSY?

There should be a compelling reason that is understandable to you (or your primary provider) to bypass available tests that can rule out the need for a biopsy.

WILL I BE PROVIDED A SAMPLE BIOPSY REPORT SO I KNOW WHAT TO EXPECT?

This should be readily available, but remember that it is a sample.

WHO WILL CONTACT ME WITH THE RESULTS?

It is helpful to understand who will contact you with the results and their familiarity with the testing results. Most geneticists will contact you directly, especially if the results are abnormal. Lab personnel, office staff, or even a General Pediatrician or primary provider may not be comfortable having a discussion with the patient/guardian regarding the results. As a result, it is helpful to understand the availability of the geneticist to discuss the information in depth.

WHEN SHOULD I EXPECT THE RESULTS?

Laboratories are required to have estimated turnaround times for their testing, so this information should be readily available.

DO YOU HAVE ANY FINANCIAL OR RESEARCH INCENTIVE TO THE TYPES OR NUMBER OF TESTS YOU ORDER?

This answer should be straightforward and concise.

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WHAT IS THE RATIO BETWEEN THE NUMBER OF PATIENTS YOU SEE AND THE SUBSEQUENT NUMBER ON WHOM YOU REQUEST BIOPSIES?

Basically, learn how often this provider is ordering biopsies as not all patients will require a biopsy, particularly as a first line of evaluation. The standard of care should be a detailed evaluation prior to ordering a biopsy.

CAN YOU PROVIDE IN WRITING THE COST OF A MUSCLE BIOPSY AND WHAT IS INCLUDED?

The answer should be concise. At the least, the cost should be within a reasonable range. To recommend a biopsy, the provider should have already reviewed your medical records to date and as such should be able to communicate their approach, with supporting reasons, to you in a way that you understand.

WHAT FACTORS WILL IMPACT THE COST OF THE BIOPSY, UP OR DOWN, IF ANY?

An answer should be concise.

WHAT FACTORS WILL IMPACT MY OUT OF POCKET EXPENSES FOR THE BIOPSY? HISTORICALLY, WHAT DOLLAR RANGE HAVE YOU SEEN PATIENTS BECOME RESPONSIBLE FOR WHEN EVERYTHING IS SAID AND DONE?

An answer should be concise.

IF ADDITIONAL TESTING OR PROCEDURES ARE REQUIRED AFTER YOU GAIN PRE-APPROVAL FROM MY INSURANCE COMPANY, WILL I BE HELD FINANCIALLY RESPONSIBLE FOR THESE COSTS?

Typically, you may become financially responsible for some of these costs depending on a number of factors such as if your insurance will authorize and cover these add-ons. Request that the provider inform you of such add-ons prior to incurring the cost so you can decide if you would like to move forward or not.

WILL YOU PROVIDE ME WITH ALL THE CONSENT FORMS BEFORE MY APPOINTMENT SO I MAY REVIEW THEM AT MY LEISURE?

Review all forms carefully so you are comfortable with all the stipulations contained in the document and if need be, consult an attorney.

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WILL YOU PROVIDE IN WRITING IF ANY REMAINING BIOPSY MATERIAL EXISTS?

You have the right to know if there is any genetic material remaining after your biopsy, but you will need to request the information as it is not standard practice to include this information within the biopsy report. Knowing this information when your biopsy report is released makes it so much easier to come by than to look for this information months, years, or decades later. Plus, without any genetic material available there is no reason to concern yourself with its security, storage, future use, and estate planning.

WILL YOU PROVIDE IN WRITING HOW I CAN HAVE MY REMAINING BIOPSY MATERIAL RELEASED TO ANOTHER FACILITY FOR STORAGE?

You have the right to unrestricted access to any of your remaining genetic material, unless you have signed documents to the contrary - so check consent forms closely before signing them.

There are storage facilities around the country that specialize in this type of storage. This prevents any unwanted research from being conducted on your genetic material. Any unwanted research may use up your genetic material that otherwise would have eliminated you/your child from having to go through either additional blood testing or another invasive biopsy if at some future date there are new breakthroughs, research, or clinical trials you wish to participate in.

If you chose to have the lab store your genetic material, they should provide you in writing exactly what the procedures are to release tissue or samples upon your request, what their normal turnaround times are to release samples, and if there are any associated fees.

Please learn how your tissue/sample will be stored. There should be reasonable backup protections such as back-up generators and/or power supplies in addition to high security settings with restricted access to only key employees, security check in/checkout policies, and other safeguards in place.

Find out how long a lab holds onto any remaining material and it is wise to include contact information within your estate planning so your estate may know where your genetic material is stored in case they ever need access to it.

WHO HAS CONTROL OVER MY GENETIC MATERIAL AND HOW MAY THEY USE IT?

Make sure you fully understand who can use and how your genetic material may be used. Be comfortable before you release ANY rights to your genetic material and if need be, consult an attorney.

DO YOU CONDUCT RESEARCH?

Participation in research requires your consent. In writing you should always have the right to opt out of any and all research without concern over how doing so may impact your care. If you do decide to participate in research, be comfortable with the stipulations within the document

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you sign. Documents requiring your signature may release rights to your genetic material and information under specifically defined terms or with no terms of any kind.

We believe much good is generated from research and encourage our patients to participate in studies, provided that they are well aware of their rights as potential research subjects.

DO YOU HAVE ANY RESEARCH INCENTIVE TO THE TYPES OR NUMBER OF TESTS YOU ORDER?

An answer should be straightforward and concise.

WHAT CONTROLS ARE IN PLACE TO SAFEGUARD MY GENETIC MATERIAL AND GENETIC DATA FROM UNWANTED RESEARCH IF I CHOSE NOT TO BE INCLUDED IN RESEARCH?

You should have the right in writing to always opt out of and to sequester/secure your genetic material from any and all research without concern. As before, there should be high security settings with restricted access to only key employees, security check in/checkout policies, and other safeguards in place.

WHAT DO I HAVE TO DO IF I CONSENT TO BE INCLUDED IN RESEARCH AT ONE POINT, BUT AT A LATER DATE WISH TO BE EXCLUDED FROM RESEARCH?

Standard practices dictates that you have the right to withdraw from research at any point. You should be provided with clear instructions on how to execute your wish to withdraw within the documents you may be required to sign.

VMP is a clinical practice and consulting firm that specializes in the evaluation and management of children & adults with rare genetic, metabolic, mitochondrial & inherited disorders. We utilize various laboratories for our testing needs. If you are interested in learning about our referral pattern, we will be happy to speak to you directly.

The information contained in this document is not intended nor should it replace a one on one discussion about your specific issues with a healthcare provider. It is not meant to be a substitute for professional one on one advice by qualified doctors, allied medical personnel, and other professional services. The responsibility for any use of this information rests with you.

Please let us know if you have further questions and/or suggestions.

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