**IBMPFD Educational Information – Patients**

**What is IBMPFD?**
IBMPFD stands for **I**nclusion **B**ody **M**yopathy associated with **P**aget's disease of bone and/or **F**rontotemporal **D**ementia. IBMPFD is a rare genetic disease with symptoms that begin in adulthood. IBMPFD can be caused by a number of genetic changes (mutations) in a gene called Valosin Containing Protein (VCP or p97). Researchers are still investigating how these mutations lead to the various symptoms of the disease.

**What are the symptoms of IBMPFD?**
The symptoms of IBMPFD appear in adulthood and progress with age. Most of the time symptoms are first recognized by doctors in the 40s and 50s, but milder symptoms may be noticed by those affected in their 20s and 30s. The symptoms progress with age and people who have the disease usually pass away in their 50s or 60s from heart problems, breathing problems, or other problems secondary to the disease. People who have IBMPFD could have problems with three main areas:

1) Muscle: Muscle wasting is the most common problem for people with IBMPFD. 80 - 90% (8 or 9 out of 10) of people with IBMPFD will have muscle weakness, usually in the hips and shoulders. Usually the muscles closer to the center of the body will be affected before the muscles that are further out along the legs and arms. This weakness increases with time and many people eventually need to use a wheelchair and other mechanical aids to help with mobility. Muscle wasting can also cause heart and breathing problems that can lead to earlier death.

2) Bone: About 50% (5 out of 10) of people with IBMPFD will have Paget's disease of bone (PDB). Bone is replaced all the time, but with PDB there are problems with this normal process. PDB causes one or more bones to grow larger and weaker. It most often affects the back, head, hips, and legs. This can lead to pain, deformity, easier breakage, and sometimes hearing loss. Some medications can lessen or slow the PDB symptoms.

3) Brain: About 30% (3 out of 10) of people with IBMPFD experience frontotemporal dementia (FTD) starting, on average, at 55 years. Dementia is a brain problem that affects a person's mental abilities, including thinking and speaking. There are different types of dementia. FTD can involve personality changes and problems with understanding and using language. Memory is usually not affected until the later stages of the disorder.

**Is there a cure, treatment, or therapy for IBMPFD**?
Unfortunately, there is no cure for IBMPFD because we do not have a way to change a person's genes. There are treatments to help lessen, delay, or eliminate some of the symptoms of PDB. There are also some therapies for maintaining quality of life for as long as possible and slowing the rate of decline.

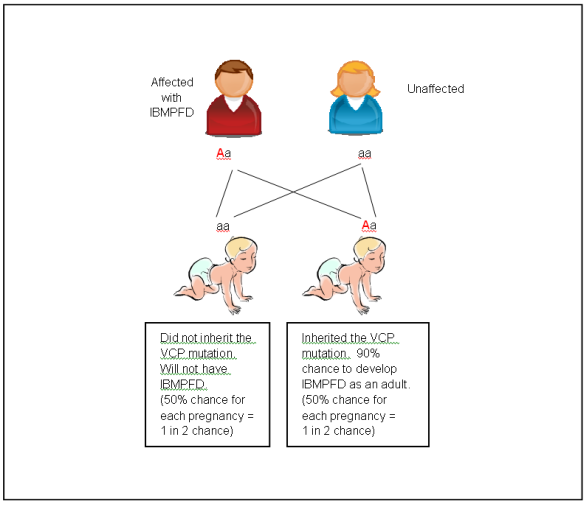
1) Muscle: There is no direct treatment for the muscle weakness. Quality of Life therapies include using assisted living devices like wheelchairs, walkers, canes, toilet lifts, and lift chairs as well as machines to help with breathing. Supportive therapies include physical therapy and stretching exercises to promote mobility and general physical health. For example, these exercises might reduce susceptibility to breathing problems and pneumonia. Research studies may be available to investigate the effects of exercise or medications.

2) Bone: Bisphosphonate medications for PDB are helpful for rebuilding normal bone. Bisphosphonate treatment is usually taken by mouth and is effective at treating the pain associated with the condition. Some drug treatments have the potential to significantly eliminate the symptoms of PDB (e.g. Reclast).

3) Brain: There is no medication that has been approved specifically to treat FTD, although your doctor may decide to prescribe medications that have been approved for other conditions. People with IBMPFD should meet with a neurologist to discuss management of dementia which might include therapies to mitigate some of the symptoms for those affected and their caregivers.

4) Other: Social and emotional support systems are often extremely valuable for patients, their caregivers, and family members.

**How is IBMPFD passed down through families?**
IBMPFD is a genetic disorder that may be passed down from parent to child. If a parent has a mutation (a genetic change that causes IBMPFD) then each of his or her children will have a 50% probability (1 in 2 chance) to inherit the mutation.




Almost everyone who inherits the mutation will have some symptoms, usually identified in the 40s or 50s. People in the same family may begin to have symptoms at different ages and some family members may have worse symptoms. For example, the disease may progress at different rates, some family members may have PDB while others do not, and different family members may have different secondary symptoms. Researchers do not completely understand yet why there can be such a difference in symptoms even between family members with the same mutation of the VCP gene. These differences may be caused by the effects of other genes that interact with VCP, differences in health habits, or other factors.

80% (8 out of 10) of people with IBMPFD have a parent with same disorder. Twenty percent (2 out of 10) of people with IBMPFD do not have a parent or other relative with the disease. For these people, it is likely that the mutation first happened in them and was not present in either of their parents. All people with IBMPFD have a 50% (1 in 2) chance of passing the mutation to each of their children.

**How does DNA testing for IBMPFD work?**
The IBMPFD gene (called VCP) is tested by comparing it with a known “normal” gene to identify genetic changes that might lead to disease. The test uses DNA from a blood sample (less than 1 tablespoon of blood).

There are two reasons that a doctor might order the VCP DNA test. First, DNA testing can confirm a diagnosis of IBMPFD for someone who symptoms of IBMPFD. Your doctor can order

either a specific test for the locations on the VCP gene where mutations have previously been found or a test for the entire VCP gene.

Second, DNA testing may also be used by people with a family history of IBMPFD who do not have symptoms and want to find out whether or not they will develop the disease in the future. If possible, it is best to first test a family member with the symptoms of IBMPFD. If the mutation that runs in a family is then known, carrier testing for other family members is much easier, less expensive, and the results are more meaningful.

If you have questions about whether genetic testing is right for you or your family members, please make an appointment with a geneticist or genetic counselor. These are professionals who specialize in inherited conditions and coordinating genetic tests. They are trained to explain genetics, genetic testing, and the implications of genetic test results.

**What is the purpose of VCP DNA testing?**
IBMPFD has often been misdiagnosed as a different disease and DNA testing is the only definite way to diagnose IBMPFD. Having an accurate diagnosis allows:

- Doctors to determine if screening tests should be ordered for PDB or other manifestations so that appropriate treatments and therapies can be prescribed
- Lifestyle changes (e.g., changes in diet, nutrition, and exercise)
- The choice to participate in research to help scientists learn more about IBMPFD
- Information about who else in the family could develop the disease
- DNA testing for family members without symptoms to find out if they have the mutation.
- Testing of a pregnancy by amniocentesis (testing some of the liquid around the pregnancy) or chorionic villus sampling (CVS: testing a small sample of the placenta)
- Preimplantation genetic diagnosis (PGD). PGD is a way of having a pregnancy that does not have an IBMPFD mutation. The sperm and egg are joined in a laboratory and the embryos have the VCP genetic test. Only embryos that do not have the familial mutation are transferred to the mother to carry to term.

**What are the risks of VCP DNA Testing?**

People who do not have any symptoms and are considering DNA testing for IBMPFD should make an appointment with a geneticist or a genetic counselor. A person must carefully think through the reasons for wanting to get the test, whether they would want to know the results, and how both positive and negative results might affect their life and the lives of other family members. Discussing the testing with a geneticist or genetic counselor will allow a fully informed decision about whether to do the test or know the results. These people are trained to release results in a way that will be most helpful and least disruptive to a person's life.

In the past there have been concerns about insurance and employment discrimination, especially for family members without any symptoms. In 2008 a law called the Genetic Information Nondiscrimination Act (GINA) was passed. This law protects people from discrimination by insurance companies and employers based on genetic information. However, this law is new and has not yet been tested in court, so the extent of GINA's protection is still not well established. Patients should still think carefully about how their DNA test result might impact their employment and insurance. A genetics professional can help to guide a person through this process.

**What does it mean if the DNA test comes back positive?**
A positive DNA result means that a mutation that causes IBMPFD was found in the VCP gene. A positive result has different meanings depending on the reason the test was ordered. For someone experiencing symptoms a positive result confirms the diagnosis of IBMPFD. For someone too young to have symptoms a positive result gives a pre-symptomatic diagnosis. A pre-symptomatic diagnosis means that there is a 90% chance that the person will experience one or more of the IBMPFD symptoms as they get older

**What does it mean if the DNA test comes back negative?**
A negative DNA result means that no mutation was found in the parts of the VCP gene that were tested. A negative result means different things depending on the reason the test was ordered.

**1) Person with symptoms of IBMPFD:** A VCP mutation has been found in about 70% (7 out of 10) of people who have symptoms of IBMPFD. The other 30% (3 out of 10) of people may have mutations that the VCP test cannot detect or they may have mutations in another gene or genes that have not been discovered by scientists yet. The lab will consult with the doctor if there are symptoms that strongly suggest IBMPFD and the test comes back negative. The lab may also be able to provide a referral for follow-up studies through a research group.

**2) Unaffected person in family with a known VCP mutation:** In this case, someone in the family who has IBMPFD has had genetic testing and a specific VCP mutation has been found. Unaffected relatives may now be tested to see if they have the same mutation. A negative result means that this person will not develop IBMPFD.

**3) Unaffected person in family with no known VCP mutation:** If no VCP mutation has been found for a family, then a negative result can only lower the chance that the person would develop IBMPFD. There is still a probability there is an unknown or undetectable mutation on the VCP gene or that the disorder in their family is the result of a mutation in another gene or genes. That is why first testing a symptomatic person in the family to find a family mutation is the preferred method of testing.

**What is a variant of unknown significance?**
A **V**ariant **O**f **U**nknown **S**ignificance is also sometimes called a VOUS. A VOUS means that a change was found in the VCP gene, but the change is not known to be harmful or not. If you have a VOUS result, the lab will discuss the implications with your doctor. The lab can also refer you to researchers who might be able to study the variant to try to learn more.

**How do I get the DNA test for IBMPFD?**
Please talk to your doctor if you are interested in learning more about genetic testing for VCP. You may also wish to see a geneticist or genetic counselor, professionals who specialize in hereditary conditions, coordinating genetic tests, as well as explaining genetics, genetic testing, and the implications of genetic test results. The test uses a blood sample (less than 1 tablespoon) and the results are available in about 3 weeks.

There are a few different ways that your doctor can order the VCP test. There are tests that look in specific sections of VCP where known mutations have previously been found or there is a test of the entire VCP gene. Please talk to your doctor about which of the tests listed below would be best for you or your family member.

**<u>Payment for testing:</u>**
Mitomed will bill your hospital or lab, which will then bill your insurance company. All insurance companies are different, so you will want to contact them to learn more about your coverage before your doctor orders the test. They will want to know the CPT (Current Procedural Terminology) codes listed below. You may receive a bill for any amount that your insurance company does not cover (e.g. your deductible). If Mitomed cannot bill your hospital or lab, we will need payment by cashier's check or money order before testing. You are responsible for contacting your insurance company about reimbursement.

**5007**: Exon 5 screening: 63% of identified mutations have been found in exon 5.
Price: 343.80 USD
CPT codes: 83891, 83898, 83894, 83904x2, 83912

**5008**: Screen of the four commonly mutated exons: All of the 10 identified mutations have been found in exons 3, 5, 6, and 10 of VCP.

Price: 802.20 USD
CPT codes: 83891, 83898x4, 83894, 83904x8, 83912

**5006:** Full sequencing of VCP gene
Price: 1719 USD for full sequencing of all exons
1544 USD if stepwise testing is ordered with exon 5 screen (total=1887.80)
1317.90 USD if stepwise testing is ordered with exon 4 screen (total =2120.10)
CPT codes: 83891, 83898, 83894, 83904x2, 83912

**9001:** Testing of a known familial mutation
Price: 326.61 USD
CPT codes: 83891, 83898, 83894, 83904x2, 83912

Mitomed does not offer pregnancy testing or PGD, but will coordinate with other laboratories to ensure that these tests are available to interested families. Mitomed does not charge for coordinating reproductive testing for mutations identified in our laboratory. This testing can be arranged through GeneDx or another laboratory chosen by you or your doctor. GeneDx charges 1500 USD for prenatal testing and requires 8 weeks advance notice to set up the test before the prenatal sample is collected.

**Where can I learn more?**
David Sweetman, a patient advocate with IBMPFD, maintains a website: www.ibmpfd.com. The website offers a message board, contact information for research groups, and a variety of other useful information for patients, caregivers, and researchers.

IBMPFD is not yet recognized by the Muscular Dystrophy Association (MDA); however, many MDA centers accept persons with IBMPFD to their programs. The muscle related symptoms and daily challenges are similar to those experienced by people with muscular dystrophy or IBM (Inclusion Body Myocitis) a disease recognized by MDA. Patients may wish to visit their website at www.mdausa.org or to call them at 1-800-FIGHT-MD (344-4863).

Genetic Counseling is recommended to explain the implications of a result to patients and their families. You can locate a genetics professional in your area through one of these organizations: GeneTests (www.genetests.org), the National Society of Genetic Counselors (www.nsgc.org), the Genetic and Rare Disease Information Center (www.genome.gov/10000409), or the Genetic Alliance (www.geneticalliance.org).

Please also feel free to contact Mitomed Diagnostic Laboratory with questions about testing. Please call 949-824-1886 or email mdl.lab@uci.edu. You can also visit our website for more information about the laboratory: http://mitomed.bio.uci.edu

**References:**

- Nat Genet. 2004 Apr; 36(4):377-81. Epub 2004 Mar 21. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein.
- GeneReview on IBMPFD at www.genetests.org


**Authors:**

This material was written collaboratively by Mitomed Diagnostic Laboratory, David Sweetman, and the research laboratory of Dr. Virginia Kimonis.


*Revised August 2008, version 2*