Dear Insurance Company Representative:

With this letter, the Malignant Hyperthermia Association of the United States (MHAUS) would like to take the opportunity to provide some background information about malignant hyperthermia (MH) and genetic testing for MH susceptibility. MHAUS is a non-profit organization committed to reducing the morbidity and mortality due to MH by improving medical care for those susceptible to MH; providing support and information for patients; and improving the scientific understanding of MH. Established in 1981, our organization has become the key resource for clinical advice and educational materials concerning the diagnosis and treatment of MH in the United States. Through the Professional Advisory Council of MHAUS, the MH hotline consultants, MHAUS has become an authoritative organizations for questions about MH and MH-like conditions.

What is MH and how can it be prevented?
MH is a dominantly inherited life-threatening syndrome triggered by commonly used anesthetic drugs. The clinical symptoms of MH such as hypermetabolism, muscle rigidity and damage, very elevated body temperature, and disturbances in cardiac rhythm may progress to serious complications such as kidney damage, blood coagulation problems, and cardiac arrest. If MH is not recognized and treated rapidly, it is likely to be fatal.

Health care professionals must be well-prepared to diagnose and treat patients who are experiencing this potentially life-threatening disorder. In addition, an integral part of MH preparedness involves taking steps to prevent its occurrence at the outset. The best way to prevent an MH episode is to identify individuals who are MH-susceptible (MHS) and develop alternate treatment plans to avoid those agents that trigger MH.

How are MHS individuals identified?
Susceptibility to MH is not readily apparent from a patient's physical appearance nor is it detectable on physical examination. The majority of MHS individuals live a normal life unless exposed to triggering agents.

An individual may be identified as MH Susceptible if he/she has experienced a clinical MH episode. In addition, because MH is inherited as an autosomal dominant trait there is a 50% chance for each child of an MHS parent to be affected and the same risk applies to siblings of an MHS individual. As such, family members of an MHS individual are considered MHS until confirmatory diagnostic testing either confirms or rules out susceptibility

Until 2005 the only available test for susceptibility involved a muscle biopsy performed in an operating room with testing in a special laboratory to assess the physiologic response to a variety of drugs that release calcium from intracellular storage sites such as caffeine and halothane, hence the test is named the caffeine-halothane contracture test, or CHCT. This test, while extremely sensitive and specific, is invasive and requires specialized equipment available in a limited number of centers. Genetic (DNA) testing is an acceptable alternative to the contracture test in certain families.

When may genetic testing be useful and thus recommended?
Genetic testing is useful where there is a high level of suspicion that the patient is at risk for an MH episode based on clinical history, results of the muscle biopsy CHCT or demonstration of a genetic change associated with MH in a family member. This determination is made through evaluation of the medical and anesthetic histories of the patient (and his/her family members) by a physician or genetic counselor. Of note, MHAUS has access to many MH experts willing to review medical/anesthetic

histories with the patient and/or their physician, in order to assist them, if desired, in making an informed decision prior to proceeding with genetic testing.

Genetic testing is also useful to confirm the diagnosis of MH susceptibility subsequent to a suspected clinical MH episode. Genetic testing is of value even though a patient may have experienced a clinical episode of MH because once a causal pathogenic variant is found in a patient other family members can be screened for the specific variant more easily and less expensively without requiring a muscle biopsy.

Thus, genetic testing may be recommended in the following situations:

- The patient has experienced an almost certain clinical episode of MH as determined by an expert in the diagnosis of MH, or the patient has a positive CHCT.
- The patient has an MHS relative who experienced an almost certain clinical episode as determined by an expert in the diagnosis of MH, or the MHS relative has a positive CHCT.
- The patient has an MHS relative with a known causal pathogenic variant.

Of note, genetic testing may be recommended in special situations where the patient either refuses to undergo a CHCT or where the patient is not eligible for a CHCT. Such situations may include cases where the patient does not meet the age or weight requirements of the biopsy center; or is tested after death.

How is genetic testing for MH susceptibility done?

Genetic testing for MH susceptibility is available in several CLIA-certified clinical laboratories in the United States. The test involves sequencing the coding region of the skeletal muscle ryanodine receptor gene (*RyR1*). This gene is considered the primary genetic locus associated with MH susceptibility; that is, most pathogenic variants causal for MH susceptibility have been found in *RyR1*. However, another gene, CACNA1S, has also been associated with MH susceptibility in a small number of patients.

Genetic testing may be performed after isolating DNA from blood, muscle or other tissue. The patient's DNA is then analyzed for the presence of *RyR1* variants, and specifically, for pathogenic variants causal for MH susceptibility.

RyR1 sequencing is usually performed in a step-wise manner, targeting the 'hot spots' where pathogenic variants are most frequent first, then proceeding to other parts of the gene if no variants are found. A partial sequencing approach may also be chosen to target a known causal pathogenic variants previously identified in the family. Next generation sequencing of the entire gene combined with targeted sequencing is also an option in certain of the CLIA-approved laboratories. Two additional genes may be included that contributes < 1% of causal pathogenic variants for MH; the *CACNA1S* gene and the *STAC*-3 gene.

What is the likelihood that genetic testing will be useful for a patient?

The likelihood that genetic testing will be useful (i.e., yield a diagnostic finding) for a patient depends upon the assessment of his/her risk for an MH episode, as well as the method of sequencing chosen. For example, in one study of individuals with positive CHCTs where *RyR1* sequencing was limited to 'hot spot' regions, 25% of the individuals were found to harbor causative pathogenic variants. However, in other studies of CHCT positive individuals up to 70% are found to harbor, one or more pathogenic DNA variants. Of note, over 400 RYR1 variants have been found in the population and a limited number have been functionally characterized thus far by the European Malignant Hyperthermia Group (EMHG; www.emhg.org) and demonstrated to be disease causing. Studies are underway to characterize the significance of the other DNA variants.

Of note, if genetic testing yields no diagnostic finding, MH susceptibility cannot be ruled out. A CHCT test (described in detail in a separate MHAUS reference document) would then be required to confirm a patient's status with regard to MH susceptibility.

What are the benefits of genetic testing?
Once a causative pathogenic variant is found, the individual is considered MHS and a muscle biopsy can be avoided. Family members can be tested for that specific causative variant. This reduces the cost of testing significantly. In addition, the patient who is diagnosed as MHS now has proof that *the specific medications can kill him/her and the patient should wear a medical identification tag to alert healthcare personnel of his/her status with respect to MH.* If this patient should need to undergo surgery, his/her family and doctors will be aware of his/her MH susceptibility and a *possible long expensive stay in the hospital or ICU* or even death can be averted.

Finally, prevention is better than a cure. Once armed with the knowledge resultant from this test, a patient can choose to pursue risk evaluation of his/her present or future children.

Patient Counseling and Consent for Genetic Testing:
MHAUS strongly recommends that, prior to ordering and performing genetic testing, the following topics be discussed during the informed consent process:

1. The benefits and potential risks of genetic testing
2. Cost of genetic testing
3. Possible need for CHCT testing
4. Possible testing of other family members
5. Risks of MH during surgery with triggering or without triggering anesthetics
6. Clinical implications for future anesthetics in MH positive individuals

In addition, MHAUS recommends that the results of genetic testing be explained to the patient by a genetic counselor, MH expert, or other appropriate health care professional.

All patients who had a positive genetic test will be advised to wear a medical identification tag and to advise other family members that they too may be at risk and should be evaluated.

Finally, if approved by the patient, the test results may be shared with the North American Malignant Hyperthermia Registry, a subsidiary of MHAUS. The Registry is essentially a database of information about MH episodes, providing a clinical correlation between clinical history, genetic, and biopsy test results (if available). The Registry provides a place where patients/families and their health care professionals can retrieve valuable medication information, communicate and store important medical histories relating to the risk for MH confidentially.

For further information regarding malignant hyperthermia and bibliographic information concerning genetic testing, please feel free to contact us at 607-674-7901.

Sincerely,

Henry Rosenberg, MD
MHAUS President