



Malignant Hyperthermia Association
of the United States

MHAUS GUIDELINES

**Testing for Malignant
Hyperthermia (MH)
Susceptibility:**

**How do I counsel
my patients?**





CONTENTS OF SLIDE SET

- **Diagnostic tests available**
- **Eligibility criteria for testing**
- **Additional test information, referrals**
- **Evaluating your patient**
- **Advising your patient**
- **MH resources & references**





Diagnostic Testing, Preface

1. Diagnostic testing options to evaluate MH susceptibility are not recommended as a screening tool for the general population.
2. Test usefulness depends on the pre-test probability that the patient is MH-susceptible (MHS).
3. Diagnostic tests are most useful when making treatment decisions for surgical patients where there is a high level of suspicion that the patient is susceptible to MH.





Diagnostic Testing, Preface (Continued)

4. Before any diagnostic testing is recommended, an evaluation of your patient's susceptibility to MH should be completed using available medical data.
5. Susceptibility to MH is inherited in an autosomal dominant fashion. Therefore, evaluation of your patient's susceptibility to MH depends upon a careful review of both your patient's and his/her family members' medical history.





Diagnostic Tests Available

1. Muscle Contracture Test: Caffeine
Halothane Contracture Test (CHCT)*
2. Genetic Testing (Ryanodine Receptor
[RYR1] gene sequencing)

* CHCT refers to the method of contracture testing performed in North America, while IVCT (In Vitro Contracture Testing) is the method of contracture testing performed in Europe and some other countries.





Muscle Contracture Testing (CHCT)

- **Gold Standard**
- Requires skeletal muscle biopsy from patient's thigh to assess muscle contractile properties upon exposure to ryanodine receptor agonists (eg. caffeine, halothane).
- **Must be performed at the MH Muscle Biopsy Center.**
- Abnormally high levels of contractile force indicate MH susceptibility.
- Sensitivity: close to 100% (false negatives are rare)
- Specificity: ~80% (~20% false positives)





Genetic Testing (RYR1 Gene Sequencing)

1. Involves isolation of DNA from patient sample (white blood, or muscle cells; or other tissue sample)
2. *Primary genetic locus associated with MH susceptibility is the ryanodine receptor (RYR1) gene; a DNA variant in the gene is characterized as:*
 - a. Unrelated polymorphism (no significant functional effect)
 - b. Causative mutation* (via functional studies)
 - c. Indeterminate (variant of unknown significance)



**Currently 29 listed MH causative RYR1 mutations (see www.emhg.org). Additional ones expected to be added to panel in near future.*



Genetic Testing Causative Mutations

1. Presence of **causative mutation*** in RYR1 gene is **diagnostic for MH susceptibility**.
2. At this point, not all proven MHS individuals have been found to harbor a **causative mutation**. The sensitivity of the genetic test depends upon several factors, including the population selected and the methodology of the testing utilized.
3. Once a **causative mutation** is found, **family members** can be tested for **that specific causative mutation**; if found, the individual is considered **MHS** and a muscle biopsy for contracture testing can be avoided.



**Currently 29 listed MH causative RYR1 mutations (see www.emhg.org). Additional ones expected to be added to panel in near future.*



Eligibility Criteria for Testing

1. CHCT Testing Indications
2. Genetic Testing Indications





CHCT Test Indications

- Patient with known MHS relative (as determined by positive muscle contracture test)
- Patient with MHS family member (as determined by past suspicious MH episode, but **without** a known RYR1 causative genetic mutation)
- Patient with past suspected MH event (wait 3-6 months post event, depending upon the degree of rhabdomyolysis)
- Patient with **severe** MMR during anesthesia with a triggering agent
- Patient with **moderate to mild** MMR with evidence of rhabdomyolysis





CHCT Test Indications (continued)

- Patient with unexplained rhabdomyolysis during or after surgery (may present as sudden cardiac arrest due to hyperkalemia)
- Patient with exercise-induced rhabdomyolysis after a negative rhabdomyolysis workup
- Signs suggestive of but not definitive for MH
- If military service is desired, patients with suspicion of MHS are required to undergo CHCT.

Note: Age and weight requirements for muscle biopsy procedure vary by Biopsy Center.





Genetic Testing Indications (U.S.)

The **indications** for **genetic testing** are more **limited** than those for **CHCT testing** because a complete panel of causative mutations (in the RYR1 gene and possibly other genes) has not yet been identified, and thus, the RYR1 test sensitivity (i.e., the percentage of individuals who test positive amongst those who are MHS) is variable (as noted in previous slides).

- Patient with a confirmed or highly suspicious clinical episode of MH
- Patient with positive CHCT
- Patient with MHS relative as determined by positive CHCT
- Patient with MHS relative as determined by a confirmed or highly suspicious clinical episode of MH
- Patients with relatives with known causal RYR1 mutation



Note: The index case or proband should always be tested first, if at all possible.



Tiered Genetic Testing

TIERED TESTING: Sequencing may be performed in a **tiered** manner due to the large size of the RYR1 gene as well as to a patient's medical history.

“Tier 1”

Partial sequencing
of gene “hot spots” to
search for known
causative mutations

“Tier 2”

Sequencing of the remaining exons (full gene) when no
causative mutation is found in “Tier 1”





Partial & Full Gene Sequencing - Indications

Partial RYR1 sequencing

- To **target** a specific causative mutation previously identified in an affected family member
- To determine presence of **known causative mutation(s)** (and other variants) in specific gene regions:
 - Best candidates are patients with highly suspicious history for MH as determined by confirmed MH episode or positive CHCT.
 - Less ideal candidates include patients with family history alone or those with MH-like event but no family history.

Full RYR1 sequencing

- To determine the presence of any variants and known mutations in patients with highly suspicious history for MH as determined by confirmed MH episode or positive CHCT, and in which there is no known causative mutation in family members





Additional Test Information, Referrals

1. CHCT
 - Pros & Cons
 - Costs & Insurance
 - Referral to MH Muscle Biopsy Centers
2. Genetic Testing
 - Pros & Cons
 - Costs & Insurance
 - Referral to Genetic Testing Laboratories





CHCT - Pros and Cons

Pros:

- Positive result establishes definitive diagnosis for patient who is tested.
- Negative result allows patient freedom of choice regarding anesthetic use, certain military career opportunities.

Cons:

- Patient must undergo **invasive** surgical procedure; 2-7 days relative disability
- Testing can only be performed in **specialized Biopsy Centers** – **patients must travel to center**
- Expensive





CHCT - Cost, Insurance

- Cost: approximately \$6000 - \$10,000
- Insurance
 - In the U.S., CHCT is covered by most insurance companies; however, it is strongly recommended that the patient contact his/her insurance carrier **prior** to biopsy procedure
 - In Canada, the cost is covered by each Provincial health plan for Canadian residents





Referral to Muscle Biopsy Center for CHCT Testing

- Biopsy Center Director, physician or genetic counselor [GC] may refer patient for diagnostic testing.
- Contact the MH Biopsy Center closest (geographically) to your patient's residence (see next slide) and request the appropriate paperwork.





*Malignant Hyperthermia Association
of the United States*

MH Muscle Biopsy Centers for CHCT Testing, U.S. and Canada

University of Minnesota

Minneapolis, MN

Paul A. Iaizzo, PhD

(612) 624-7912 or -3959

iaizz001@umn.edu

www.vhlab.umn.edu/mh/index.html

University of California

Davis, CA

Timothy Tautz, MD

(530) 752-7805

timothy.tautz@ucdmc.ucdavis.edu

Uniformed Services University

of the Health Sciences

Bethesda, MD

(Military & Civilian)

Sheila M. Muldoon, MD

(301) 295-3532

smuldoon@usuhs.mil

Wake Forest University

Winston-Salem, NC

Joseph R. Tobin, MD

(336) 716-4498

jtobin@wfubmc.edu





Genetic Testing - Pros and Cons

Pros:

- Less expensive than CHCT
- Less invasive than CHCT
- No need to travel
- If causative mutation found in family member, other family members can have predictive testing carried out with a high degree of accuracy, without the need for CHCT, and at a lower cost than the first person tested.

Cons:

- Due to discordance (contracture result \neq genetic testing result), plus the heterogeneity of MH, absence of a causative mutation does not rule out MH susceptibility; muscle contracture test would be needed to confirm the individual is not susceptible to MH
- Expensive
- Insurance may not cover





Genetic Testing - Cost, Insurance

- Cost: approximately \$800-\$4000 (partial → full gene sequencing); in certain cases, only one exon may be sequenced for ~ \$200.
- Insurance: some insurance companies will cover the cost of the test; many need to be educated about MH and the validity of genetic testing for MHS. MHAUS can help to communicate this information to the insurance company.
- MHAUS may be able to provide financial assistance for patients who are candidates for genetic testing. Contact MHAUS for more information info@mhaus.org





Referral for Genetic Testing

- Physician or genetic counselor [GC] may refer patient for additional diagnostic testing.
- Contact one of the Genetic Testing Laboratories (see next slide) and request the appropriate paperwork.





Malignant Hyperthermia Association
of the United States

Genetic Testing Laboratories

RYR1 Gene Sequencing currently available at **2** accredited
molecular genetics laboratories in the U.S.

PreventionGenetics, LLC*

**3700 Downwind Drive
Marshfield, WI 54449**

www.preventiongenetics.com

715 387-0484

[clinicaltesting@](mailto:clinicaltesting@preventiongenetics.com)

preventiongenetics.com

Center for Medical Genetics

**University of Pittsburgh Medical Center
S701 Scaife Hall**

3550 Terrace Street

Pittsburgh PA 15213

<http://path.upmc.edu/divisions/mdx/diagnostics.html>

800 454-8155 or 412 648-8519 (laboratory)



***Full gene sequencing currently offered by Prevention Genetics only.**



Evaluating your patient

1. Review indicators of MH susceptibility
2. Assess level of suspicion for susceptibility to MH
3. Review eligibility criteria for diagnostic testing
4. Consult with MH expert, if necessary





Indicators of MH Susceptibility

1.

**Suspicious
MH event data in
patient/family
members**



2.

**Possible
predisposing
factors to MH in
patient/family
members**





Suspicious MH Event Data

Look for the following possible **clinical manifestations** in association with the use of a triggering anesthetic or the depolarizing agent, succinylcholine:

As a result of increased myoplasmic calcium concentration:

- Masseter muscle rigidity
- Generalized muscle rigidity

As a result of hypermetabolism:

- Hypercapnia
- Hypoxemia
- Tachycardia
- Acidosis
- Heat production

As a result of rhabdomyolysis:

- Increased serum CK and K⁺ concentrations
- Cardiac arrhythmia
- Myoglobinuria
- Renal failure





Suspicious MH Event Data (continued)

MH Clinical Grading Scale (Larach et al., 1994) can be helpful for evaluation of data and **is based on assessment of:**

Criteria within 6 processes

1. Muscle rigidity
2. Muscle breakdown
3. Respiratory acidosis
4. Temperature increase
5. Cardiac involvement
6. Family history



Other criteria (not part of a single process)

- Base deficit
- pH
- Outcome if dantrolene was used





Suspicious MH Event Data (continued)

MH Clinical Grading Scale

- Assists in determining if MH episode has occurred
- Raw score is calculated based on fulfillment of criteria in each of the processes (noted on previous slide)
- Assistance in calculating a raw score is available through MH experts affiliated with MHAUS

NOTE: The VALIDITY of the clinical grading scale increases when data is obtained for each process. Thus, the scale may underestimate the probability of MH if certain data are not available. In addition, the circumstances of the event must be taken into consideration (eg. time of occurrence of certain symptoms during the perioperative period).





Possible Predisposing Factors to MH susceptibility (MHS)

HI

Association of Factor with MHS

LOW

- Known MH-susceptible (MHS) relative as determined by positive CHCT or genetic test, or as determined by confirmed or highly suspicious clinical episode
- Presence of Central Core Disease (CCD)*
- Presence of MultiminiCore Disease (MmD)*
- History of unexplained fevers that have been thoroughly evaluated without diagnosis
- Previous episode of rhabdomyolysis that has been thoroughly evaluated without diagnosis
- History of dark-colored urine
- History of heat stroke

* Patients with CCD, MmD, and other myopathies may have a higher risk for an MH or MH-like episode. Such patients should be evaluated by a neurologist prior to providing treatment and/or diagnostic testing recommendations.





Evaluating your patient (continued)

1. Review indicators of MH susceptibility
2. Assess level of suspicion for susceptibility to MH
3. Review eligibility criteria for diagnostic testing
4. Consult with MH expert, if necessary





Advising your patient

1. Testing
2. Precautions: testing in patients with muscle disorders
3. Lifestyle issues
4. Genetic counseling (GC)
5. Sample Cases





Testing

- After careful review of medical data, diagnostic test indications, and consultation with an MH expert (if necessary), communicate your recommendations with respect to appropriate testing options to the patient.
- Follow up with the patient and appropriate testing center regarding the patient's test results for future treatment management.
- Encourage your patient to seek support from Genetic Counselors, MHAUS and to register with the North American Malignant Hyperthermia Registry (NAMHR) (*see Resource section for more information*).





Precautions: testing in patients with muscle disorders

Patients with CCD, MmD, and other myopathies such as Duchenne's or Becker's muscular dystrophies may have a higher risk for an MH or MH-like episode upon exposure to a triggering anesthetic agent. Such patients should be evaluated by a neurologist prior to providing treatment and/or diagnostic testing recommendations

- CCD, MmD associated with MH susceptibility
- Patients with Duchenne's or Becker's muscular dystrophies are at risk for hyperkalemic cardiac arrest with succinylcholine or other MH triggering agents (but this is NOT MH)
- Individuals with any form of myotonia should not receive succinylcholine





Life Style Issues

- Muscle cramping and possibly heat stroke may be more common in MHS patients. Further study needed.
- MHS individuals may be advised to avoid extremes of heat but NOT to restrict athletic activity unless they have overt rhabdomyolysis.
- Advice should be personalized to the patient based on consultation with an MH expert.





Genetic Counseling (GC)

GC may be a useful adjunct to patient-physician discussions and may help to:

- » Determine the best person in the family to offer RYR1 testing
- » Explain the autosomal dominant pattern of inheritance for MHS (***see next slide***)
- » Discuss test results and help communicate with family members
- » Discuss potential implications re: health/life insurance and impact of GINA, a law recently passed which protects patients from discrimination on the basis of genetic testing results
- » Reinforce availability of MHAUS as resource, importance of communication with HCPs, use of medical-alert ID bracelet





Autosomal dominant inheritance pattern, risk to family members:

Biologic Parents of
Proband:
50% risk unless
proband has a *de novo*
mutation



Other family members-
depends on status of
proband's parents

MHS
Proband

Sibs: **50% risk IF**
parents are MHS



Offspring: **50%**
chance of
inheriting MHS





Sample Cases

CASES

1. Patient with CHCT+ family history
2. Patient with possible clinical episode of MH (eg., fever post-op)
3. Patient with a known MH mutation in family
4. Patient with highly suspicious clinical MH episode.

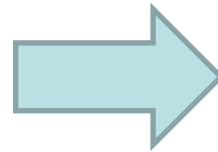




Sample Cases

CASE

1. Patient with CHCT+ family history
2. Patient with possible clinical episode of MH (eg., fever post-op)
3. Patient with a known MH mutation in family
4. Patient with highly suspicious clinical MH episode.



TESTING

1. Advise regarding genetic testing; CHCT first if patient is willing.
2. Review of medical records alone may provide diagnosis. If not, refer to Biopsy Center for CHCT testing.
3. Test for that mutation first.
4. Genetic testing is OK; CHCT first if patient is willing.





Malignant Hyperthermia Association
of the United States

MH resources & references

- Malignant Hyperthermia Association of the United States (MHAUS)
- North American Malignant Hyperthermia Registry (NAMHR)
- Genetic Counseling (GC)
- References





*Malignant Hyperthermia Association
of the United States*

Malignant Hyperthermia Association of the United States (MHAUS)

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Sherburne, NY 13460 -1069

- Phone 1-800-986-4287 or 607-674-7901
- Fax 607-674-7910
- Email: info@mhaus.org
- Website: www.mhaus.org
- Hotline for Medical Professionals: 1-800-644-9737





Malignant Hyperthermia Association
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The North American Malignant Hyperthermia Registry of MHAUS

Director, Dr. Barbara Brandom

1-888-274-7899

<https://www.mhreg.org/>

- Subsidiary of MHAUS
- Database which records detailed events surrounding MH episodes as well as clinical correlation between clinical history, genetic, and biopsy test results
- Approved by the IRB of the University of Pittsburgh Medical Center
- The Registry holds a certificate of confidentiality, reflective of its commitment to protect subject confidentiality
- Patients and physicians can provide Registry with clinical history – thus the Registry acts as a **service** for patients/families and their health care professionals to communicate and store important medical histories relating to the risk for MH.





Malignant Hyperthermia Association
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Genetic Counseling

To find a Genetic Counselor in your area, contact:

National Society of Genetic Counselors

401 N. Michigan Avenue

Chicago, IL 60611

Phone: 312-321-6834 Fax: 312-673-6972

E-mail: nsgc@nsgc.org

Web www.nsgc.org

NOTE: Deanna Steele, Genetic Counselor, affiliated with Genetic Testing Lab at the University of Pittsburgh Medical Center #800-454-8155, available to discuss genetic testing with interested patients and physicians





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