

## Genomic Testing (Secondary Findings) ACT Sheet *RYR1* and *CACNA1S* Pathogenic Variants (Malignant Hyperthermia)

Known pathogenic or likely pathogenic variants (mutations) in the *RYR1* (ryanodine receptor type 1) gene or *CACNA1S* (muscle calcium channel) gene may result in familial malignant hyperthermia (MH), a condition triggered by exposure to certain drugs used in general anesthesia including inhalation anesthetics and succinylcholine. Some pathogenic variants in the *CACNA1S* gene cause a different condition, hypokalemic periodic paralysis.

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### **YOU SHOULD TAKE THE FOLLOWING ACTIONS:**

- Inform the individual (or parent/guardian) of the genomic screening result and high risk of malignant hyperthermia from general anesthesia.
- Obtain and review family and medical history. Evaluate the patient.
- Refer for genetic counseling.
- Patient needs to be instructed to inform the anesthesia team of high risk for malignant hyperthermia prior to any procedure requiring anesthesia.

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**Clinical Considerations:** Malignant hyperthermia is a disorder in which affected individuals have few or no symptoms until exposed to volatile anesthetic gases and/or succinylcholine used in general anesthesia. Cardiovascular collapse and death can occur if not rapidly treated. Local anesthetics are considered safe. Rare individuals with malignant hyperthermia may become symptomatic with strenuous exercise or exposure to extreme heat. Treatment is to avoid exposure to the causative anesthetic agents, succinylcholine, or triggering environments. The screen-positive individual should inform the anesthesiologist/anesthetist of the presence of the variant prior to undergoing any general anesthesia. As many as 50% of those with malignant hyperthermia pathogenic variants may not develop malignant hyperthermia when exposed (nonpenetrance), however, the response to any given episode of anesthesia is unpredictable.

**Mode of Inheritance:** Malignant hyperthermia has an autosomal dominant pattern of inheritance. It is important that immediate and extended family members be offered genetic testing for malignant hyperthermia. Mutations in the *RYR1* gene are found in 70% - 80% of malignant hyperthermia cases while 1% involve the *CACNA1S* gene expressed in a skeletal muscle calcium channel.

### **Additional Information:**

[GeneReviews](#)  
[Medline Plus](#)  
[ClinGen Actionability Report](#)

### **Referral (local, state, regional and national):**

[Testing](#)  
[Find Genetic Services](#)  
[MH clinical network](#)

Disclaimer: This guideline is designed primarily as an educational resource for clinicians to help them provide quality medical care. It should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. Adherence to this guideline does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this guideline. Clinicians also are advised to take notice of the date this guideline was adopted, and to consider other medical and scientific information that become available after that date.

**LOCAL RESOURCES:** Insert local website links

State Resource site *(insert website information)*

Name

URL

Comments

Local Resource Site *(insert local and regional website information)*

Name

URL

Comments

**APPENDIX: Resources with Full URL Addresses**

*Additional Information:*

Gene Reviews

<https://www.ncbi.nlm.nih.gov/books/NBK1146/>

Medline Plus

<https://medlineplus.gov/genetics/condition/malignant-hyperthermia/>

ClinGen Actionability Report

<https://actionability.clinicalgenome.org/ac/Adult/ui/stg2SummaryRpt?doc=AC076>

*Referral (local, state, regional and national):*

Testing

<https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=RYR1>

Find Genetic Services

<https://clinics.acmg.net>

MH Clinical Network

<https://www.mhaus.org/patients-and-families/prepreport/>

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