



Geisinger

# **Implementing RYR1 and CACNA1S Results to Prevent Malignant Hyperthermia**

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# Outline

1. Genetic Information That Can Inform Medication Selection
2. Malignant Hyperthermia: Genes and Background
3. Geisinger MyCode Implementation of MHS Results
4. Discuss Proposed Implementation Guides for Upcoming CPIC Guideline

# Traditional Pharmacogenomic Markers → Actionable Genetic Markers of Disease

## Traditional Markers

Influence PK/PD

Majority of CPIC  
guidelines

Enzymes:  
CYPs, VKORC1,  
UGT/UDP, G6PD,  
TPMT, DPYD

Transporters:  
SLCO1B1

# Traditional Pharmacogenomic Markers → Actionable Genetic Markers of Disease

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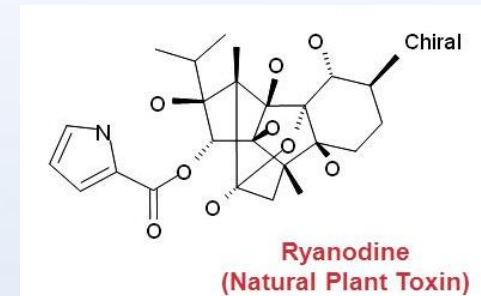
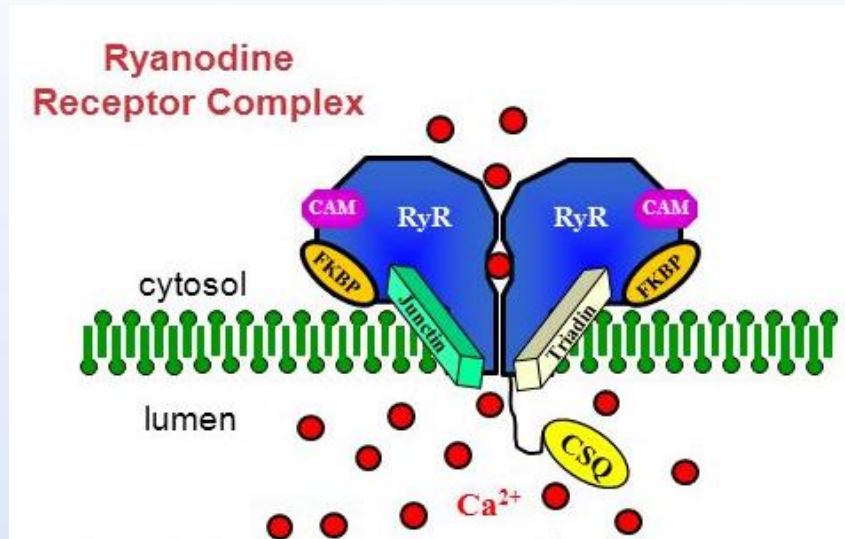
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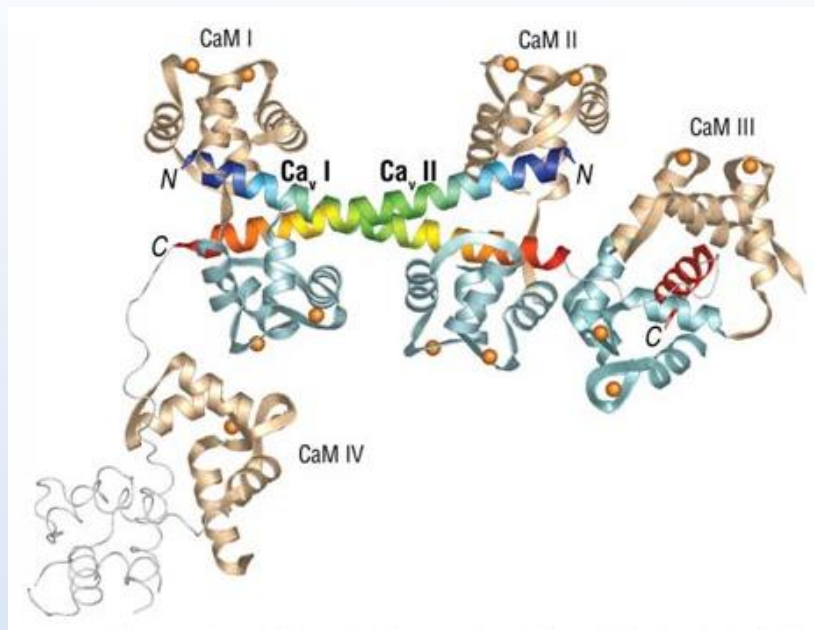
# **Malignant Hyperthermia: Genes and Background**

# RyR1: Ryanodine Receptor – Type 1



- Calcium Channel – sarcoplasmic reticulum
- Regulates release of stored calcium from sarcoplasmic reticulum
- Involved in muscle contraction

# CACNA1S: Calcium Voltage-Gated Channel subunit alpha 1S



- L-type Calcium Channel – skeletal muscle cell surface
- Upstream activator of RYR1 channels
- Involved in muscle contraction

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MH is a rare, life-threatening hypercatabolic state that is usually triggered by exposure to certain drugs used for general anesthesia or intubations

- Signs / Symptoms: muscle rigidity,  $\uparrow$  CO<sub>2</sub> production, very high temperature,  $\uparrow$  HR,  $\uparrow$  RR, mixed acidosis, rhabdomyolysis
- Occurs in 1 in 5,000 to 50,000 instances
- Mortality rates range from 6.5% to 16.9%
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Not all patients with MH are found to harbor a causative MHS mutation  
[EMHG](#) – Currently lists 42 Diagnostic MHS Mutations

# Malignant Hyperthermia Triggering Agents

## **Not safe for use in MH-susceptible patients...**

The following anesthetic agents are known triggers of MH:

- **Inhaled General Anesthetics**
- **Desflurane**
- **Enflurane**
- **Ether**
- **Halothane**
- **Isoflurane**
- **Methoxyflurane**
- **Sevoflurane**
- **Succinylcholine (warning)**

All other anesthetic agents outside of these two categories of Volatile anesthetic agents and depolarizing muscle relaxants are considered safe.

# Challenges of Implementing MHS Markers from a Pharmacogenomics Framework

1) Potentially Fatal Reaction

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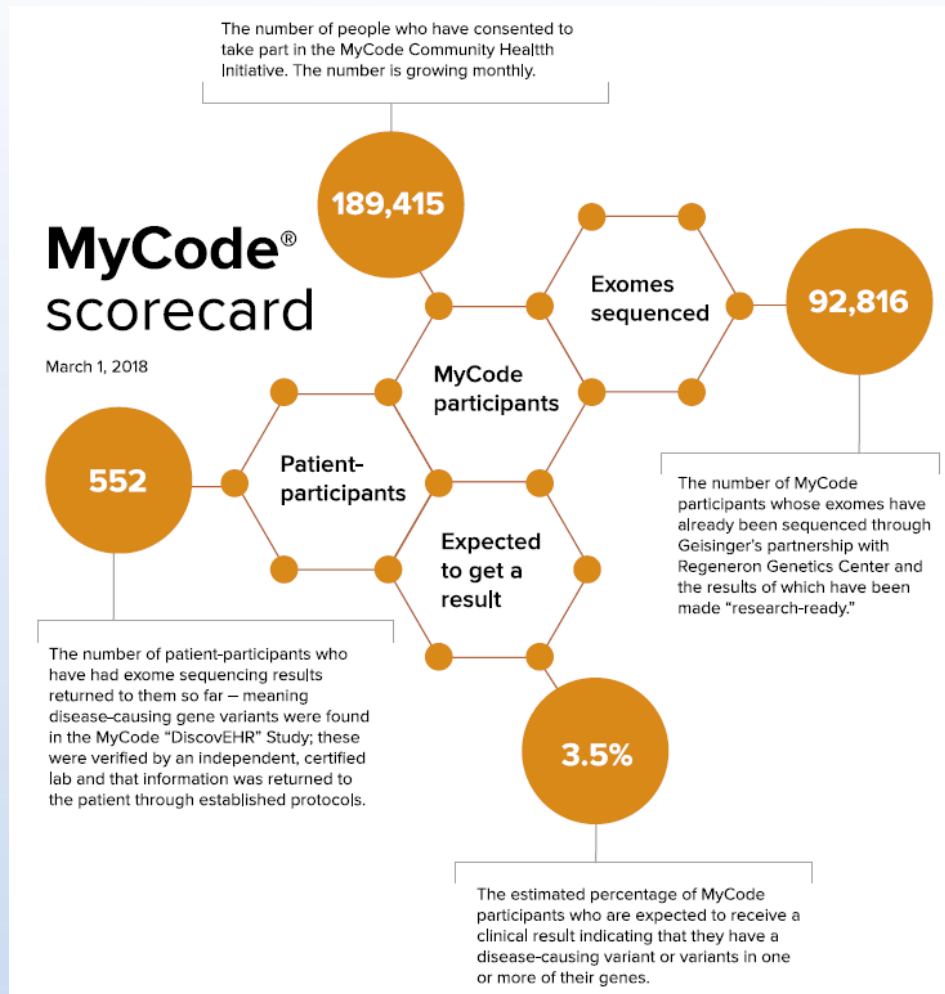
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# Challenges of Implementing MH Markers from a Pharmacogenomics Framework

- 1) Potentially Fatal Reaction
- 2) Orders for triggering agents generally do not go through standard pharmacy work flows
- 3) Triggering agents may be used in an emergent situation during which a patient may not be responsive

# **Geisinger MyCode & Implementation of MHS Results**

# Geisinger MyCode







# Geisinger MyCode

## MyCode® results returned

552 patient-participants have received results\* from the Genomic Screening and Counseling Program

For the latest results, see [go.geisinger.org/results](http://go.geisinger.org/results).

March 1, 2018

Risk condition 	Patients per risk condition 	Gene 	Patients per gene 
<b>Other</b>			
<b>Malignant hyperthermia</b> (life-threatening condition usually triggered by exposure to certain drugs used for general anesthesia)	<b>22</b>	<b>RYR1</b>	<b>22</b>

[March Genomic Screening & Counseling Update](#)

# Geisinger MH Marker Implementation – Problem List Documentation

For patients with personal or family history of Malignant Hyperthermia – Documentation as MH condition in problem list

Example ICD-10 Code: T88.3XXA Malignant Hyperthermia  
Allows for MediSpan alerting based on diagnosis code

For others who have not had a personal or family history of an MH event: Document genetic finding as a monoallelic mutation with notation of specific variant

Example ICD-10 Code: Z15.89; Monoallelic Mutation of RYR1  
Working on a back end solution to link our standardized MyCode mutation documentation to this back end alerting

# Geisinger MH Marker Implementation – “Allergy” Documentation

- Halothane
- Succinylcholine

Analogous to abacavir suggestions in the Guidelines for the Use of Antiretroviral Agents

- Same limitations / drawbacks persist

Working on “locking” these allergy field entries from editing

# Geisinger Anesthesia Evaluation

<b>Sleep Apnea Screen</b> (+/-) sleep apnea	<b>Kidney/Bladder/Prostate</b> (+/-) kidney/bladder/prostate ROS
<b>Pulmonary</b> (+/-) history of tobacco use (+/-) URI within last 3 weeks (+/-) COPD(+/-)asthma	<b>Neuro/Psych</b> (+/-) seizures (+/-) TIA/CVA
<b>Cardiovascular History</b> ACC/AHA Functional Capacity: (+/-) hyperlipidemia (+/-) hypertension (+/-) pacemaker (+/-) AICD (+/-) CAD (+/-) prior MI (+/-) CABG/stent/PTCA/valve surgery (+/-) dysrhythmias (+/-) Beta-Blocker therapy	<b>Musculoskeletal</b>  Comments:
<b>Cardiac Review of Systems</b> (+/-) chest pain, tightness, or pressure (+/-) DOE (+/-) PND (+/-) orthopnea (+/-) syncope	<b>Cancer</b>  Comments:
<b>Metabolic/Diabetes/Pregnancy</b> (+/-) thyroid disease (+/-) type II diabetes (+/-) chronic steroid use (+/-) parathyroid disease (+/-) adrenal disease (+/-) pituitary disease	<b>Infectious Disease Screen</b>  Comments
<b>Hematology</b> (+/-) anemia (+/-) bleeding problem (+/-) anticoagulation / coagulopathy	<b>Pediatric Specific (less than 18 yo)</b>
<b>Gastrointestinal</b> (+/-) reflux (+/-) hiatal hernia (+/-) gastric or duodenal ulcer (+/-) liver disease (+/-) pancreatic disease	<b>Anesthesia History</b> (+/-) PONV <b>(+/-) malignant hyperthermia</b> (+/-) history of anesthetic complications (+/-) allergy to soy or peanut products (+/-) motion sickness

# **Proposed Implementation Guides for Upcoming RYR1 / CACNA1S CPIC Guideline**

# RYR1 / CACNA1S Guideline

## Draft Implementation Text

Test Result	Coded Genotype / Phenotype Summary	EHR Priority Result Notification	Consultation (Interpretation) Text Provided with Test Result
Negative	Uncertain Susceptibility	Normal Risk	Variation in RYR1 and/or CACNA1S genes is associated with increased risk of Malignant hyperthermia after administration of depolarizing muscle relaxants and potent volatile anesthetics. Although no known causative RYR1 or CACNA1S variants were detected in this patient, it should be noted that this negative finding does not absolutely rule out the possibility of malignant hyperthermia. These results should be interpreted in the context of clinical findings, family history and other laboratory data.
Flagged RYR1 or CACNA1S Variant Found	Malignant Hyperthermia Susceptible	Priority / High Risk	This result signifies that this patient has one copy of [RYR1 or CACNA1S variant]. Patients with this genotype are associated with malignant hyperthermia susceptibility and should <b>NOT</b> receive potent volatile anesthetics or depolarizing anesthetics.

a This table is provided to show examples of how a test result could be translated into discrete fields within an EHR, including a brief interpretation that summarized the result. The information presented here is consistent with the guideline but may need to be adapted to a given EHR's design and capabilities. Various EHRs or organizations may require different terms, and so different options are provided.

b Genetic tests for RYR1 and CACNA1S are reported as specific mutations.

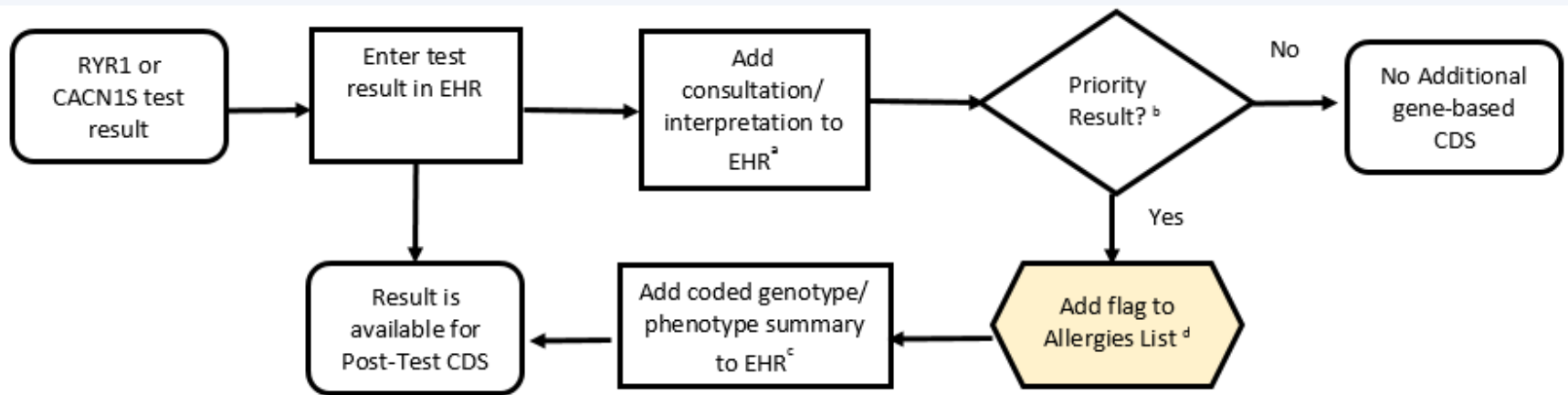
c The coded genotype/phenotype summary is used to store an interpretation of the test result. This is a design decision that may differ among sites.

d For this example, a priority result is defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.

e The specific wording of the interpretive text may differ among sites.

# RYR1 / CACNA1S Guideline

## Proposed Workflow, Clinical Implementation



a See Supplementary Table for diplotype/phenotype specific example

b "Priority result" is defined as a genetic test result that necessitates a change in drug, drug dose, or drug monitoring now or potentially in the future.

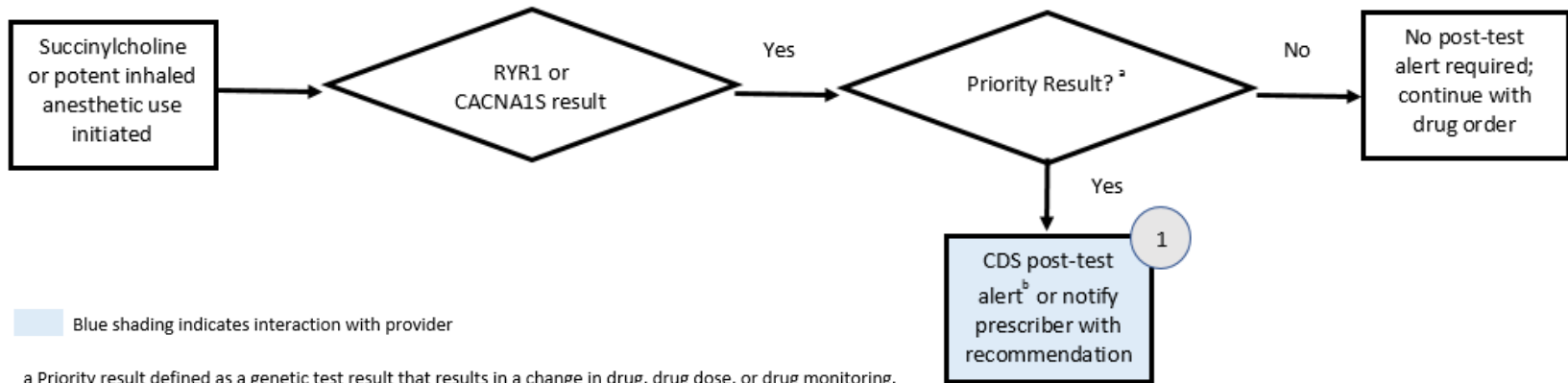
c Documentation in the EHR is institution specific. Optimally, the phenotype and/or genotype are available in the EHR to permanently

inform prescribing decisions. See Supplementary Table S7 for genotype/phenotype-specific summaries.

**d Malignant Hyperthermia is a potentially fatal drug interaction and should be treated on par with anaphylaxis**

# RYR1 / CACNA1S Guideline

## Proposed Workflow, Point of Care



Blue shading indicates interaction with provider

<sup>a</sup> Priority result defined as a genetic test result that results in a change in drug, drug dose, or drug monitoring.  
<sup>b</sup> See Supplementary Table for diplotype /phenotype specific post-test alert example.

Flow Chart Reference Point <sup>a</sup>	CDS Context, Relative to Genetic Testing	Trigger Condition	CDS Alert Text
1	Post-Test	Malignant hyperthermia susceptibility identified	Based on genotype, this patient is predicted to be malignant hyperthermia susceptible. Do not use volatile anesthetics or depolarizing muscle relaxants. Choose alternative anesthetics. Please consult an anesthesiologist or clinical pharmacist <sup>b</sup> for more information.

<sup>a</sup> The specific wording of the alert text may differ among sites.

<sup>b</sup> Pharmacist, pharmacologist, or a clinician with pharmacogenetic or malignant hyperthermia expertise/training.