



Geisinger

Implementing RYR1 and CACNA1S Results to Prevent Malignant Hyperthermia

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Outline

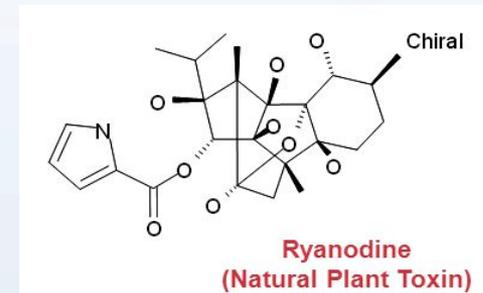
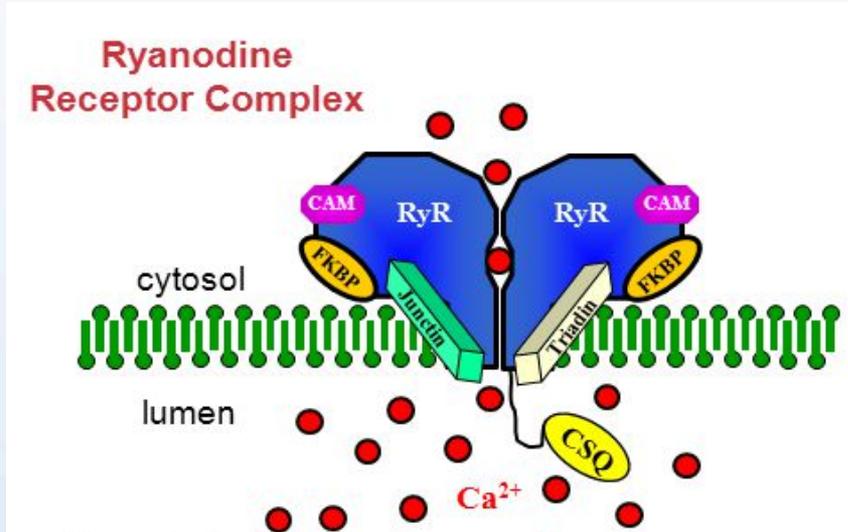
1. Malignant Hyperthermia: Genes and Background
2. Geisinger MyCode Implementation of MHS Results
3. Discuss Proposed Implementation Guides for Upcoming CPIC Guideline

Malignant Hyperthermia: Genes and Background

Malignant Hyperthermia Susceptibility

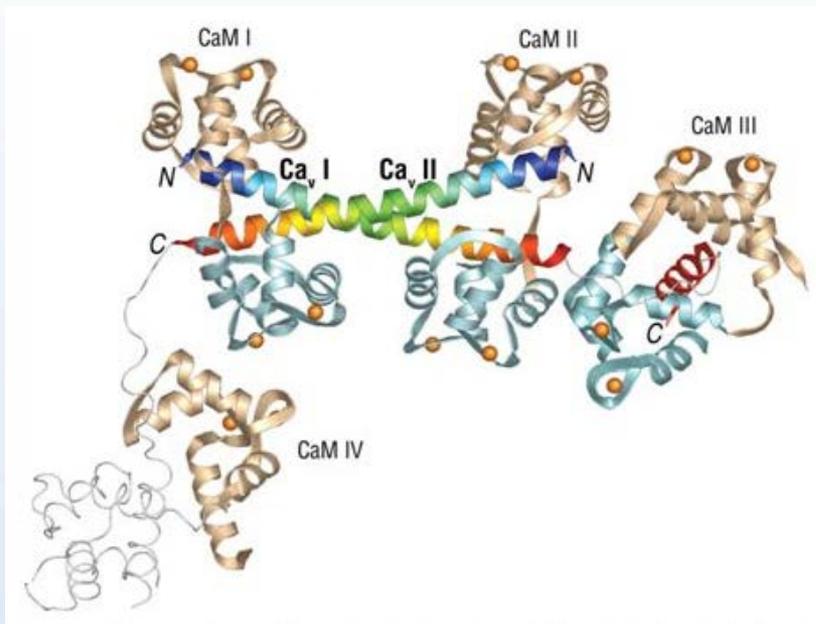
Malignant Hyperthermia Susceptibility (MHS) is a rare autosomal dominant trait associated with mutations in RYR1 and CACNA1S

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

Malignant Hyperthermia Susceptibility

Malignant Hyperthermia Susceptibility (MHS) is a rare autosomal dominant trait associated with mutations in RYR1 and CACNA1S

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 CO₂ 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%
- Can manifest up to 24 hours after exposure
- Antidote / Treatment = Dantrolene (muscle relaxant)
 - continual infusion (36 vials / 70kg pat)

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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.

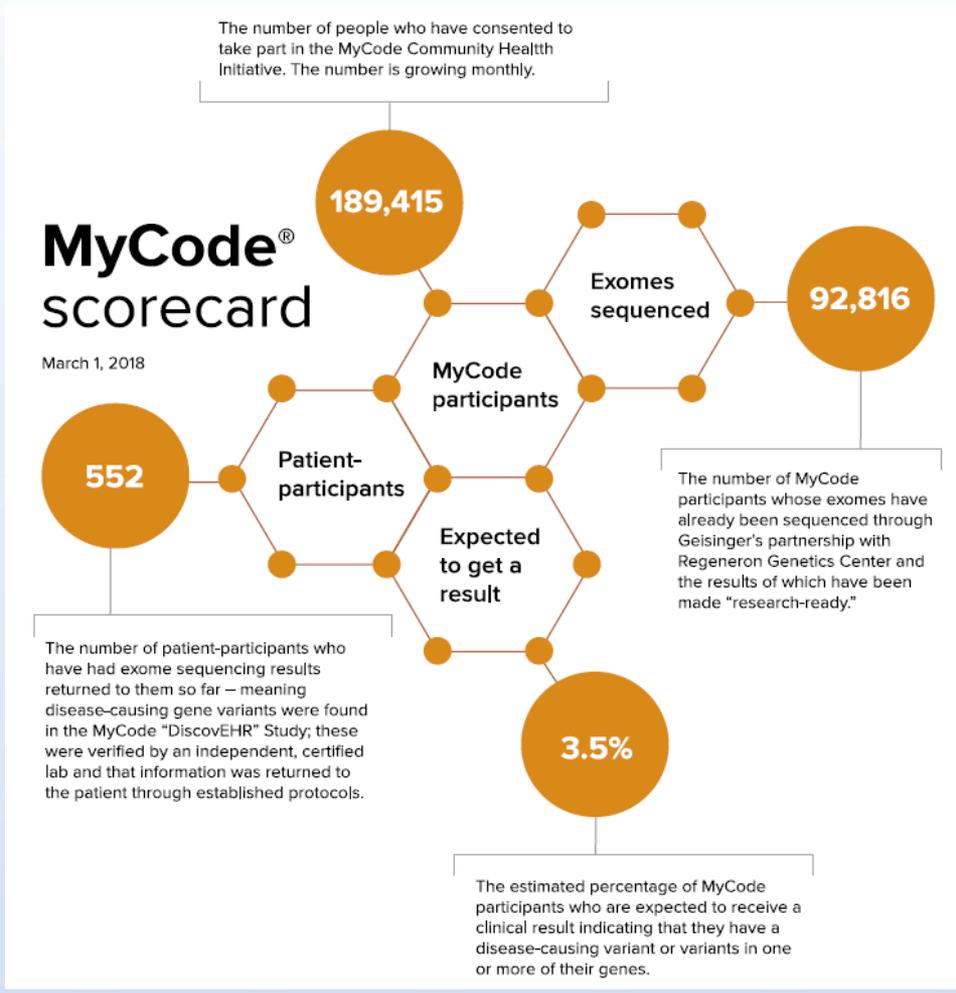
Challenges of Implementing MH Markers from a Pharmacogenomics Framework

Orders for triggering agents generally do not go through standard pharmacy work flows

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.



150,000+
PARTICIPANTS

March 1, 2018

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

[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 (most cross reactive via Epic alerts)
- 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

Sleep Apnea Screen (+/-) sleep apnea	Kidney/Bladder/Prostate (+/-) kidney/bladder/prostate ROS
Pulmonary (+/-) history of tobacco use (+/-) URI within last 3 weeks (+/-) COPD(+/-)asthma	Neuro/Psych (+/-) seizures (+/-) TIA/CVA
Cardiovascular History ACC/AHA Functional Capacity: (+/-) hyperlipidemia (+/-) hypertension (+/-) pacemaker (+/-) AICD (+/-) CAD (+/-) prior MI (+/-) CABG/stent/PTCA/valve surgery (+/-) dysrhythmias (+/-) Beta-Blocker therapy	Musculoskeletal Comments:
Cardiac Review of Systems (+/-) chest pain, tightness, or pressure (+/-) DOE (+/-) PND (+/-) orthopnea (+/-) syncope	Cancer Comments:
Metabolic/Diabetes/Pregnancy (+/-) thyroid disease (+/-) type II diabetes (+/-) chronic steroid use (+/-) parathyroid disease (+/-) adrenal disease (+/-) pituitary disease	Infectious Disease Screen Comments
Hematology (+/-) anemia (+/-) bleeding problem (+/-) anticoagulation / coagulopathy	Pediatric Specific (less than 18 yo)
Gastrointestinal (+/-) reflux (+/-) hiatal hernia (+/-) gastric or duodenal ulcer (+/-) liver disease (+/-) pancreatic disease	Anesthesia History (+/-) PONV (+/-) malignant hyperthermia (+/-) 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 NOT 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.

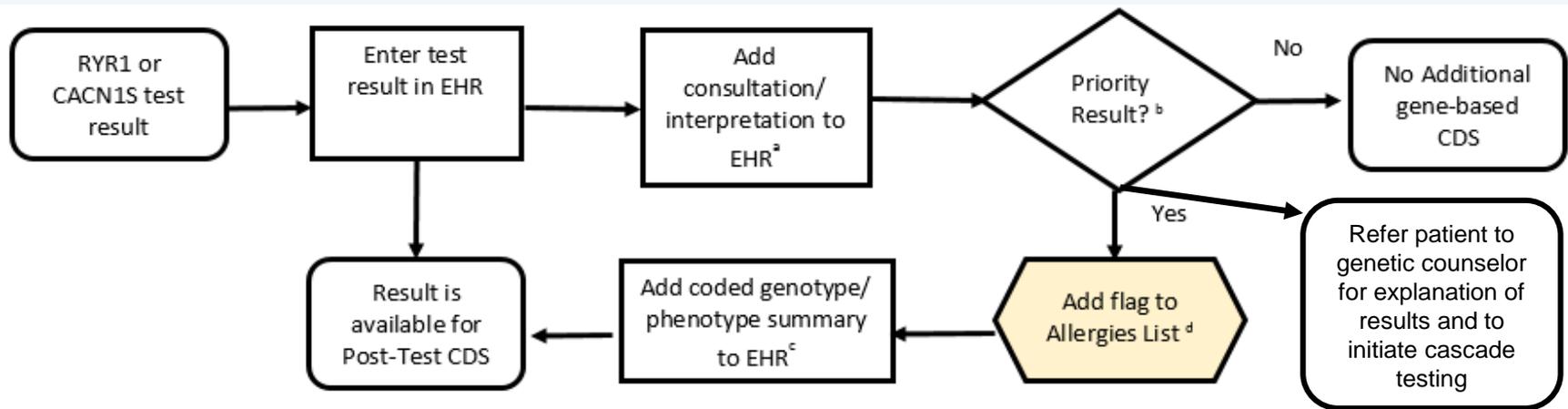
c The coded genotype/phenotype summary is used to store an interpretation of the test result. This is a design decision that may differ among sites.

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.

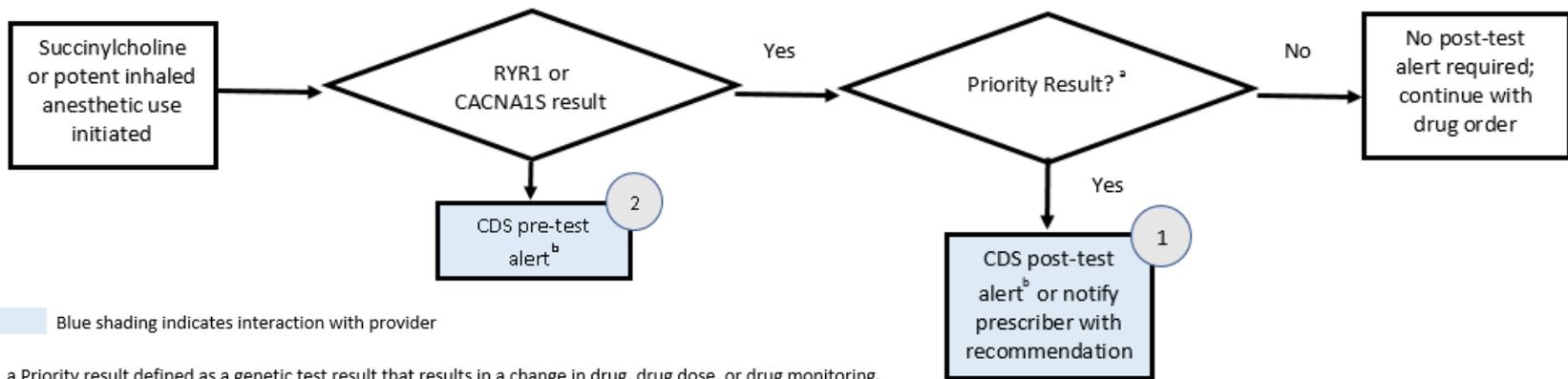
c Documentation in the EHR is institution specific. Optimally, the phenotype and/or genotype are available in the EHR to permanently

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

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

Flow Chart Reference Point ^a	CDS Context, Relative to Genetic Testing	Trigger Condition	CDS Alert Text
1	Post-Test	Malignant Hyperthermia Susceptibility Documented	Based on genotype, this patient is predicted to be malignant hyperthermia susceptible. Do not use halogenated volatile anesthetics or depolarizing muscle relaxants. Choose an alternative anesthetic. Please consult an anesthesiologist or clinical pharmacist for more information. ^b
2	Pre-Test	No RYR1 or CACNA1S Result on File	Malignant Hyperthermia Susceptibility is an inherited trait linked to changes within the RYR1 and CACNA1S genes. Genetic testing can help to guide anesthetic agent use.

^a The specific wording of the alert text may differ among sites.

^b Pharmacist, pharmacologist, or a clinician with pharmacogenetic or malignant hyperthermia expertise/training.

Integration into Clinical Workflows

Workflow	Goal of Intervention
Pre-op Assessment	Explain influence of genetics on anesthesia outcomes.
OR Suite / Anesthesia Module of EHR	Inform anesthetic use within the operating suite in real time
Post-op Observation	Inform the care of patients following anesthesia
Inpatient Admission	Identify patients with priority results to raise awareness of MHS among staff caring for patient
Emergency Intubation	Alert providers to MHS following exposure to succinylcholine to guide patient monitoring
Primary Care	Inform of new result and potential role for genetic counseling

Questions?