Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for the Use of Potent Volatile Anesthetic Agents and Succinylcholine in the Context of *RYR1* or *CACNA1S* Genotypes

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The identification in a patient of 1 of the 50 variants in the *RYR1* or *CACNA1S* genes reviewed here should lead to a presumption of malignant hyperthermia susceptibility (MHS). MHS can lead to life-threatening reactions to potent volatile anesthetic agents or succinylcholine. We summarize evidence from the literature supporting this association and provide therapeutic recommendations for the use of these agents in patients with these *RYR1* or *CACNA1S* variants (updates at https://cpicpgx.org/guidelines and www.pharmgkb.org).

The purpose of this Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline is to provide information to allow the interpretation of selected *RYR1* and *CACNA1S* genotype results so they can guide healthcare providers on the proper use of potent volatile anesthetic agents or the depolarizing muscle relaxant, succinylcholine, when such genotyping results are available. These guidelines focus on the clinical utility of the identification of variants in these genes in individuals without a personal or family history of a reaction to these drugs or agents. Detailed guidelines for use of these agents, diagnostic testing, as well as analyses of cost effectiveness, are beyond the scope of this paper. CPIC guidelines are periodically updated at www.cpicpgx.org.

FOCUSED LITERATURE REVIEW

A systematic literature review, focused on *RYR1* and *CACNA1S* genotypes and potent volatile anesthetics and depolarizing muscle relaxants use was conducted (details in **Supplementary Material S1**). The literature review focused on 48 *RYR1* and 2 *CACNA1S* variants accepted as "diagnostic mutations" by the European Malignant Hyperthermia Group (EMHG) (https://www.emhg.org/diagnostic-mutations).

DRUGS: HALOGENATED VOLATILE ANESTHETICS AND DEPOLARIZING MUSCLE RELAXANTS

Background

Potent volatile anesthetic agents are widely used and generally safe agents for inducing general anesthesia. The mechanism of action of these agents is unknown in spite of many hypotheses and investigations. The agents include sevoflurane, halothane, enflurane, isoflurane, methoxyflurane, and desflurane; all of the currently available potent inhalation anesthetics are presumed to be equivalent triggers of malignant hyperthermia (MH).

Depolarizing muscle relaxants bind to postsynaptic acetylcholine receptors of the neuromuscular junction causing channel opening that leads to initial activation followed by sustained depolarization of the muscle membrane with profound muscle relaxation in patients undergoing intubation and many surgical procedures. Succinylcholine (also known as suxamethonium) is the one depolarizing muscle relaxant that is known to be a potential triggering agent for an MH reaction.

Unlike many actionable pharmacogenetic traits that affect the metabolism and/or excretion of a drug, the variants in the genes under consideration here predispose individuals to a severe and

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sometimes lethal hypermetabolic reaction to a number of anesthetic pharmacologic agents. Although pharmacogenetic variants related to the metabolism of these drugs have been identified (e.g., butyrylcholinesterase and succinylcholine[1]), this evidence review focuses on the MH reaction.

GENES: *RYR1* AND *CACNA1S*

Background

RYR1. The ~160 kb *RYR1* gene encodes the ~560 kDa ryanodine receptor isoform 1 protein (RYR1 or RyR1).[2] The RYR1 protein, a subunit of the homotetrameric calcium release channel, is embedded in the sarcoplasmic reticulum membrane. Homotetrameric calcium release channels are present in many cell types, but RYR1-mediated calcium release predominantly manifests in skeletal muscle fibers where it plays a crucial role in excitation-contraction coupling, the process by which depolarization of the sarcolemma results in calcium release from the sarcoplasmic reticulum to trigger muscle contraction.[3]

The *RYR1* gene is the primary locus (~ 70% of individuals with malignant hyperthermia susceptibility (MHS)) for the pharmacogenetic trait of MHS. This trait is a predisposition to a hypermetabolic reaction triggered by any of the potent volatile anesthetics (except nitrous oxide and xenon) or the depolarizing muscle relaxant succinylcholine.[4–6] Upon exposure of an MH-susceptible person to a triggering agent, there can be a sustained increase of cytoplasmic calcium within skeletal muscle fibers, which leads to uncontrolled muscle contractions. The most sensitive and early indicators of MH are tachycardia and an increase in end-tidal CO_2 followed by skeletal muscle rigidity, metabolic and respiratory acidosis, and hyperkalemia, hyperthermia, and arrhythmia. If succinylcholine was administered, masseter muscle rigidity is often the first sign of MH.[5] If left untreated, an MH reaction can result in cardiac arrest and death.[4] Any of the potent volatile anesthetics, and the depolarizing muscle relaxant succinylcholine, can trigger an MH reaction in susceptible individuals.[5] Potent volatile anesthetics and succinylcholine are contraindicated in individuals with MHS. MH episodes have an estimated incidence of between 1/10,000 and 1/250,000 anesthesias. The prevalence of the MHS genetic trait has been estimated to be between 1/2,000 and 1/3,000.[7,8] The true incidence of MHS is difficult to establish, as screening for the susceptibility is challenging and the majority of susceptible individuals are phenotypically normal unless exposed to an MH triggering agent. To further complicate matters, not all exposures to a triggering agent in an individual with MHS will lead to an MH reaction.

The diagnosis of MHS is made by one of two criteria: (i) positive response to an *in vitro* muscle bioassay, such as the *in vitro* contracture test (IVCT), or the caffeine-halothane contracture test (CHCT), as it is known in the United States; or (ii) the presence of a pathogenic variant in *RYR1* or *CACNA1S* found by molecular genetic testing (*RYR1* gene definition table[9]). It is also important to recognize that the American College of Medical Genetics and Genomics has included *RYR1* and *CACNA1S* in its list of genes for which pathogenic variants should be returned as secondary findings.[10]

Although one can make a clinical diagnosis of MH based on the presenting phenotype,[11] the IVCT/CHCT or a molecular diagnosis is considered definitive. Both the CHCT and IVCT require a muscle biopsy to measure muscle contraction induced by varying concentrations of caffeine or halothane.[12,13] Not only does access to the test vary by country, the test can also be difficult to perform, as it requires a muscle biopsy under regional anesthesia using nontriggering anesthetics at a specialized MH biopsy testing center. The sensitivity of the contracture test is high, so negative results rule out a diagnosis of MH.[14] However, if the contracture results are positive, the results should be followed up with genetic testing to determine the causative *RYR1* or *CACNA1S* variant so other family members can be informed and subsequently tested.[4]

MHS is inherited in an autosomal-dominant pattern, and a heterozygous genotype of a pathogenic variant in *RYR1* can be considered as diagnostic for the trait. The *RYR1* variants associated with MHS perturb the RYR1 channel function in a dominant gain-of-function mechanism, making mutant RYR1 channels more sensitive to activation. The exact mechanism by which MHS pathogenic variants cause MHS is not known but current evidence strongly suggests that these variants render RYR1 channels hypersensitive to activation by depolarization and pharmacologic agonists, including volatile anesthetics.[15,16]

Molecular genetic testing for these variants can be challenging to interpret due to the large size of the gene and the >2,700 variants in the coding region that have been identified (http://exac.broadinstitute.org/gene/ENSG00000196218, accessed August 24, 2018), most of which (about 1,700) are missense variants. Testing is also complicated by the locus heterogeneity and the fact that several of the loci have not been characterized. The EMHG, a consortium of the European MH researchers, maintains a list of 47 single-nucleotide variants and one small deletion (c.7042_7044delGAG; p.Glu2348del) in *RYR1* (see table; https://www.emhg.org/diagnostic-mutations; accessed March 8, 2018) that are designated "diagnostic MH mutations"—frequently referred to as "causative mutations" in publications[4,17]—based on expert review). A person with one of the pathogenic variants in *RYR1* listed here we consider to have MHS (**Table 1**; **Table S1**[9]).

CACNA1S. The second locus for MHS is the *CACNA1S* gene encoding the α_{1S} subunit of the dihydropyridine receptor, located in the sarcolemma, which functions as the voltage-sensor that is mechanically coupled to and activates RYR1 channels when the sarcolemma is depolarized.[3,18] Like *RYR1*, *CACNA1S*-related MHS is inherited in an autosomal dominant pattern. Although the *CACNA1S* gene is not as large or polymorphic as *RYR1*, it still has several variants, and interpretation of these variants can be challenging. Unlike *RYR1*, *CACNA1S* variants are an uncommon cause of MHS, as only about 1% of patients with MHS have pathogenic variants in *CACNA1S*. The EMHG list includes only two variants in *CACNA1S* that have been determined to be "MHS causative" (https://www.emhg.org/diagnostic-mutations; accessed March 8, 2018; **Table S1**; *CACNA1S* allele definition table[9]).

Genetic test interpretation

In contrast to many pharmacogenetic tests, there are no star alleles nor diplotypes to be considered for MHS testing. Instead, as noted above, MHS is inherited in an autosomal dominant pattern, and the pathogenic variants are rare, typically missense substitutions present in the heterozygous state in one of the two associated genes (RYR1 and CACNA1S frequency table[9]). The distinction of a pathogenic variant from a benign variant in these genes is complex and based on numerous and heterogeneous pieces of evidence, such as functional data, genetic data, *in silico* predictions, case control data, population data, and other factors. For these reasons, we have determined that the initial CPIC recommendations should start from the assessments provided by the EMHG consortium, which has evaluated much of these data to arrive at a list of 50 variants that can be considered "diagnostic mutations." Here, we supplemented the EMHG evaluations with evidence from publications from our literature review that supports the pathogenicity of these variants (**Table S1**). In doing so, we recognize that not all 50 of these variants have equally strong evidence to support pathogenicity, and these differences are noted in the tables below. Because the EMHG does not provide the exact criteria they used to evaluate each case or list the studies they used in the evaluation of an *RYR1* variant, we, therefore, had to rely on a literature search and an assessment of the applicable studies. We endeavored to develop a guideline that could start the process of thinking about *RYR1* variants, similar to what CPIC did with *G6PD*.[19] Some in the MH research field have begun an evaluation of all of the reported disease-causing *RYR1* variants, which will likely take several years of effort—and broad input from the field—to develop methods and a consensus on the process. These pathogenicity assertions, from the wider research community review, can then be used for future recommendations. In this way, newly emergent knowledge can then expand the list of comparatively more proven *RYR1* variants. Of note, the lack of inclusion of a variant in this paper should not be interpreted to mean that we have judged them to be benign.

This CPIC recommendation is based on the assumption that genetic testing has been performed and that one of the 50 listed variants has been detected, irrespective of the methodology of that testing. It is critical to recognize that although a positive result for one of these 50 variants is straightforward to interpret, a result that is negative, or a result that detects a variant that is not among the 50 listed here, is more difficult to interpret. Because of the locus and allelic heterogeneity of MHS, such a result must be interpreted with caution.[20] In such cases, the interpreting clinician must take into account the personal and family history of MH and MHS, previous genetic, and/or *in vitro* MHS testing that has been performed and other factors to arrive at a conclusion based on all available evidence. This recommendation is primarily directed at the scenario of an individual without a known personal or family history of MHS, who does not have a myopathy and who is found on testing to have one of the 50 listed variants. The interpretation of a negative genetic testing result in an at-risk individual, who is related to a person with MHS and a pathogenic variant, is complex and controversial and is outside the scope of this recommendation.

Available genetic test options

Molecular genetic testing of *RYR1* and *CACNA1S* is available from numerous clinical testing laboratories (see Genetic Testing Registry: https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=RYR1.)

Incidental findings

Some of the 48 *RYR1* variants described here have also been found in individuals with *RYR1*-related myopathies.[21–25] Pathogenic variants in *RYR1* can cause several other inherited muscle disorders, such as central core disease, multiminicore disease, congenital fiber type disproportion, centronuclear myopathy, King-Denborough syndrome, nemaline myopathy, and congenital myopathy with cores and rods.[22,26–30] Some of the congenital myopathies are inherited in an autosomal-dominant pattern and others in an autosomal recessive pattern.[28] These disorders typically manifest as symptomatic myopathies and should be diagnosed and managed by a neuromuscular specialist. These recommendations do not address the use of inhaled anesthetic agents or succinylcholine in such patients.

There is some evidence that certain variants in *RYR1*, including some of the 48 on the EMHG list (e.g., c.1840C>T; p.(Arg614Cys)), may increase the risk of rhabdomyolysis in individuals taking statins for hypercholesterolemia.[31]

Other considerations

STAC3 myopathy (also referred to as Native American myopathy) is an autosomal recessive disorder caused by mutations in the *STAC3* gene. STAC3 myopathy is characterized by congenital muscle weakness, dysmorphic facial features, cleft palate, ptosis, short stature, scoliosis/kyphosis, and susceptibility to MH. Thus, potent volatile anesthetics and succinylcholine should be avoided, and nontriggering anesthetic agents should be used in patients with STAC3 myopathy/Native American myopathy.[32–37] Current data are insufficient to determine if individuals with an *STAC3* variant who do not have STAC3 myopathy have MHS.

Linking genetic variability to variability in drug-related phenotypes

There is substantial evidence linking pathogenic variants in *RYR1* and *CACNA1S* to the MHS phenotype (see **Table S1**). Application of a grading system to evidence linking genotypic to phenotypic variability indicates a high quality of evidence for a large majority of the variants listed here (**Table S1**). In general, a combination of contractility testing (i.e., IVCT or CHCT), functional data (e.g., calcium studies), and genetic data provide the basis for most of the recommendations in **Table 2**. As noted above, the CHCT and the IVCT are considered the clinical standard for the confirmation of a suspected diagnosis of MHS in a patient. For many of these 50 variants, extensive correlative work has been performed to link the putative variants in either *RYR1* or *CACNA1S* to abnormal results from the "gold standard" *in vitro* contractility assays.

Therapeutic recommendations

The critical pharmacogenetics recommendation for a person with MHS, that is, a person who is found to have one of the 50 variants described here, is that the above-noted potent volatile anesthetics

Table 1 Assignment of *RYR1* and *CACNA1S* phenotype based on genotype

Likely phenotype	Genotypes	Example variants
MHS	An individual heterozygous[a] for an *RYR1* or *CACNA1S* MH causative variant as designated by the EMHG[b,c,d]	*RYR1* c.103T>C; p.(Cys35Arg) *RYR1* c.130C>T; p.(Arg44Cys) *RYR1* c.487C>T; p.(Arg163Cys) *RYR1* c.488G>T; p.(Arg163Leu) *RYR1* c.742G>A>C; p.(Gly248Arg) *RYR1* c.982C>T; p.(Arg328Trp) *RYR1* c.1021G>C; p.(Gly341Arg) *RYR1* c.1021G>A; p.(Gly341Arg) *RYR1* c.1201C>T; p.(Arg401Cys) *RYR1* c.1209C>G; p.(Ile403Met) *RYR1* c.1565A>C; p.(Try522Ser) *RYR1* c.1589G>A; p.(Arg530His) *RYR1* c.1597C>T; p.(Arg533Cys) *RYR1* c.1598G>A; p.(Arg533His) *RYR1* c.1654C>T; p.(Arg552Trp) *RYR1* c.1840C>T; p.(Arg614Cys) *RYR1* c.1841G>T; p.(Arg614Leu) *RYR1* c.6487C>T; p.(Arg2163Cys) *RYR1* c.6488G>A; p.(Arg2163His) *RYR1* c.6502G>A; p.(Val2168Met) *RYR1* c.6617C>G; p.(Thr2206Arg) *RYR1* c.6617C>T; p.(Thr2206Met) *RYR1* c.7007G>A; p.(Arg2336His) *RYR1* c.7039_7041delGAG/*RYR1* c.7042_7044delGAG; p.(Glu2348del) *RYR1* c.7048G>A; p.(Ala2350Thr) *RYR1* c.7063C>T; p.(Arg2355Trp) *RYR1* c.7124G>C; p.(Gly2375Ala) *RYR1* c.7282G>A; p.(Ala2428Thr) *RYR1* c.7300G>A; p.(Gly2434Arg) *RYR1* c.7304G>A; p.(Arg2435His) *RYR1* c.7354C>T; p.(Arg2452Trp) *RYR1* c.7360C>T; p.(Arg2454Cys) *RYR1* c.7361G>A; p.(Arg2454His) *RYR1* c.7372C>T; p.(Arg2458Cys) *RYR1* c.7373G>A; p.(Arg2458His) *RYR1* c.7522C>G; p.(Arg2508Gly) *RYR1* c.7522C>T; p.(Arg2508Cys) *RYR1* c.7523G>A; p.(Arg2508His) *RYR1* c.9310G>A; p.(Glu3104Lys) *RYR1* c.11969G>T; p.(Gly3990Val) *RYR1* c.14387A>G; p.(Try4796Cys) *RYR1* c.14477C>T; p.(Thr4826Ile) *RYR1* c.14497C>T; p.(His4833Tyr) *RYR1* c.14512C>G; p.(Leu4838Val) *RYR1* c.14545G>A; p.(Val4849Ile) *RYR1* c.14582G>A; p.(Arg4861His) *RYR1* c.14693T>C; p.(Ile4898Thr) CACNA1S c.520C>T; p.(Arg174Trp) CACNA1S c.3257G>A; p.(Arg1086His)
Uncertain susceptibility	An individual negative for an *RYR1* or *CACNA1S* malignant hyperthermia–causative variant as designated by the EMHG[b,c,d]	—

EMHG, European Malignant Hyperthermia Group; MH, malignant hyperthermia; MHS, malignant hyperthermia susceptibility.
[a]Individuals who have biallelic (homozygous or compound heterozygous) pathogenic variants in *RYR1* generally will have autosomal recessive myopathies and should be managed according to the standard of care for those disorders. Although some may, indeed, have susceptibility to anesthetic agents, the recommendations described here cannot adequately address such patients, and they should be managed by a physician who is knowledgeable regarding those disorders. [b]https://www.emhg.org/diagnostic-mutations (accessed March 8, 2018). [c]A negative or inconclusive genetic test cannot be assumed to indicate normal *RYR1*-related phenotype and should be interpreted in context of clinical findings, family history, and other laboratory data. [d]It is recognized that clinical laboratories and treating physicians can make a determination that a variant not evaluated by EMHG is pathogenic.

and succinylcholine are relatively contraindicated. Only nontriggering anesthetic agents should be used in any individual thought to have MHS. Regional anesthesia (e.g., neuraxial, peripheral nerve block, or local anesthesia), or nontriggering agent general anesthesia, should be used—avoiding all potent volatile anesthetics and succinylcholine—and after proper preparation of the

anesthetic equipment to clear it of triggering agents (see https://www.mhaus.org/mhau001/assets/File/Recommendations%20-%20With%20Table%20of%20Contents%20for%20Website.pdf for details). Nondepolarizing neuromuscular blocking drugs do not seem to trigger MH.[6] The MH-triggering agents are the potent, volatile inhaled anesthetics (e.g., desflurane, enflurane, halothane, isoflurane, methoxyflurane, and sevoflurane) and the depolarizing muscle relaxant succinylcholine; all other nondepolarizing muscle relaxants, prolonged inhalational anesthesia with nontriggering agents, and all intravenous inducing agents are alternatives not associated with MH.[4] See reference for full list of recommended and contraindicated anesthetics for use in patients with MHS.[38]

An individual negative for an *RYR1*-associated or *CACNA1S*-associated malignant hyperthermia "diagnostic mutation," as designated by the EMHG, should be considered to have uncertain susceptibility (**Table 1**). A negative result does not eliminate the chance that this patient is susceptible to MH. The genetic cause of about half of all MH survivors, with MH susceptibility confirmed by contracture test, remains unknown.[8] As such, a negative or inconclusive genetic test cannot be assumed to indicate normal *RYR1*-related phenotype and should be interpreted in context of clinical findings, family history, and other laboratory data.

Pediatrics. There is less experience with MHS in children as compared with adults, but unpublished observations suggest that the risk of an MH reaction may be higher when an anesthetic is administered in childhood.[17] The identification of a causative variant associated with MHS in a parent should lead to complete evaluation of all at-risk family members, including children. Genetic cascade testing may be sufficient to determine the MHS status of relatives. However, there is some controversy regarding the risk status of individuals who test negative for the familial variant. In addition, the complementary roles of IVCT or CHCT and genetic testing are not fully determined. These issues should be addressed in each family by an expert in the genetics of MHS. Triggering agents are relatively contraindicated (i.e., these agents should almost never be used) in all patients with MHS, regardless of age.

If the father of an expectant couple has MHS, the fetus has a 50% risk of having MHS even if the mother does not. This should be considered when anesthetizing a pregnant patient. Although there are no known cases of a fetus developing an MH crisis from an *in utero* exposure to a triggering agent, it is recommended to use a nontriggering agent if a pregnant woman carrying a potentially MHS fetus requires general anesthesia. Examples of alternatives include a local, nerve block, epidural, spinal anesthesia, or a total intravenous general anesthetic.[17] During labor and delivery, continuous epidural analgesia is recommended.[17]

Recommendations for incidental findings

Individuals with muscle diseases caused by, or associated with, genetic abnormalities in *RYR1* receptors (or less often the dihydropyridine receptor) should be treated as MH-susceptible and should be managed by the anesthesiologist in consultation with an expert in these rare neuromuscular diseases.

Other considerations

Implementation of this guideline. The guideline supplement contains resources that can be used within electronic health records to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see Resources to Incorporate Pharmacogenetics Into an Electronic Health Record With Clinical Decision Support sections of **Supplementary Material S1**).

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The identification of an individual as having MHS through genetic testing has enormous potential to reduce morbidity and mortality by the avoidance of an MH event. It is widely recognized

Table 2 Recommended therapeutic use of inhaled anesthetics and succinylcholine in relation to *RYR1* and *CACNA1S* phenotype

RYR1 or *CACNA1S* phenotype	Implications for phenotypic measures	Dosing recommendations for inhaled anesthetics or succinylcholine	Classification of recommendations[a]
MHS	Individuals are at increased risk of developing malignant hyperthermia if administered halogenated volatile anesthetics or the depolarizing muscle relaxant succinylcholine[b]	Halogenated volatile anesthetics or depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances in which the benefits outweigh the risks. In general, alternative anesthetics are widely available and effective in patients with MHS	Strong
Uncertain susceptibility	These results do not eliminate the chance that this patient is susceptible to MH. The genetic cause of about half of all MH survivors, with MH susceptibility confirmed by contracture test, remains unknown[8]	Clinical findings, family history, further genetic testing, and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants	Strong

MH, malignant hyperthermia; MHS, malignant hyperthermia susceptibility.
[a]See supplementary material S1, section **STRENGTH OF RECOMMENDATIONS**.
[b]A list of unsafe halogenated volatile anesthetics or depolarizing muscle relaxants and alternative anesthetics can be found at http://www.mhaus.org/healthcare-professionals/be-prepared/safe-and-unsafe-anesthetics.

that such events, especially if unexpected, can lead to serious medical complications with a morbidity rate as high as 35%[39] and a mortality rate at 12% for a fulminant MH reaction.[40]

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

It is important to recognize that the absence of 1 of the 50 variants delineated here does not reduce the likelihood of an MH event when compared with the general population or in an individual who has not had such testing. Said differently, the testing approach described here has a high positive predictive value but very poor sensitivity. Therefore, clinicians must properly interpret and use both positive and negative results (the presence or absence of 1 of these 50 variants), as there can be major risks to patients if these genetic test results are misinterpreted.

Halogenated volatile anesthetics or depolarizing muscle relaxants are relatively contraindicated in persons with MHS. They should not be used, except in extraordinary circumstances in which the benefits outweigh the risks. In general, alternative anesthetics are widely available and effective in patients with MHS.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Supplementary Material S1. Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for the use of potent volatile anesthetic agents and succinylcholine in the context of *RYR1* or *CACNA1S* genotypes.
Table S1. RYR1 Excel files.

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CONFLICTS OF INTEREST

L.G.B. receives salary from the NIH, is a member of the Illumina Corporation medical ethics board, and receives royalties from Genentech.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are updated periodically on https://cpicpgx.org/guidelines/ and it is the responsibility of the guideline user to consult this website for updates. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. The CPIC assumes no responsibility for any injury to persons or damage to property related to any use of the CPIC guidelines or for any errors or omissions.

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