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Allele Function and Phenotype Terms Standardization Part II

Extension to non-drug metabolizing enzymes, non-transporters, non-HLA genes

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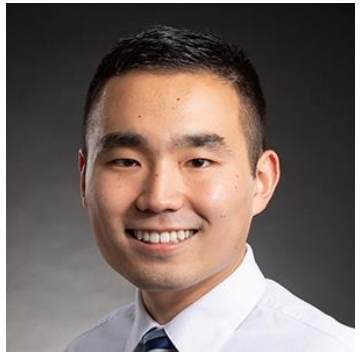

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Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

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Introduction: Reporting and sharing pharmacogenetic test results across clinical laboratories and electronic health records is a crucial step toward the implementation of clinical pharmacogenetics, but allele function and phenotype terms are not standardized. Our goal was to develop terms that can be broadly applied to characterize pharmacogenetic allele function and inferred phenotypes.

Materials and methods: Terms currently used by genetic testing laboratories and in the literature were identified. The Clinical Pharmacogenetics Implementation Consortium (CPIC) used the Delphi method to obtain a consensus and agree on uniform terms among pharmacogenetic experts.

Results: Experts with diverse involvement in at least one area of pharmacogenetics (clinicians, researchers, genetic testing laboratorians, pharmacogenetics implementers, and clinical informaticians; $n = 58$) participated. After completion of five surveys, a consensus (>70%) was reached with 90% of experts agreeing to the final sets of pharmacogenetic terms.

Discussion: The proposed standardized pharmacogenetic terms will improve the understanding and interpretation of pharmacogenetic tests and reduce confusion by maintaining consistent nomenclature. These standard terms can also facilitate pharmacogenetic data sharing across diverse electronic health care record systems with clinical decision support.

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Key Words: CPIC; nomenclature; pharmacogenetics; pharmacogenomics; terminology

Table 2 Final consensus terms for allele functional status and phenotype

Term/gene category	Final term[a]	Functional definition	Genetic definition	Example diplotypes/alleles
Allele functional status: all genes	Increased function	Function greater than normal function	N/A	*CYP2C19*17*
	Normal function	Fully functional/wild-type	N/A	*CYP2C19*1*
	Decreased function	Function less than normal function	N/A	*CYP2C19*9*
	No function	Nonfunctional	N/A	*CYP2C19*2*
	Unknown function	No literature describing function or the allele is novel	N/A	*CYP2C19*29*
	Uncertain function	Literature supporting function is conflicting or weak	N/A	*CYP2C19*12*
Phenotype: drug-metabolizing enzymes (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1)	Ultrarapid metabolizer	Increased enzyme activity compared to rapid metabolizers	Two increased function alleles, or more than 2 normal function alleles	*CYP2C19*17/*17* *CYP2D6*1/*1XN*
	Rapid metabolizer	Increased enzyme activity compared to normal metabolizers but less than ultrarapid metabolizers	Combinations of normal function and increased function alleles	*CYP2C19*1/*17*
	Normal metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles	*CYP2C19*1/*1*
	Intermediate metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles	*CYP2C19*1/*2*
	Poor metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles	*CYP2C19*2/*2*
Phenotype: transporters (SLCO1B1)	Increased function	Increased transporter function compared to normal function.	One or more increased function alleles	*SLCO1B1*1/*14*
	Normal function	Fully functional transporter function	Combinations of normal function and/or decreased function alleles	*SLCO1B1*1/*1*
	Decreased function	Decreased transporter function (function between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles	*SLCO1B1*1/*5*
	Poor function	Little to no transporter function	Combination of no function alleles and/or decreased function alleles	*SLCO1B1*5/*5*
Phenotype: high-risk genotype status (*HLA-B*)	Positive	Detection of high-risk allele	Homozygous or heterozygous for high-risk allele	*HLA-B*15:02*
	Negative	High-risk allele not detected	No copies of high-risk allele	

[a]All terms should begin with the gene name (e.g., CYP2D6 Poor metabolizer, TPMT Normal metabolizer, SLCO1B1 decreased function).

Caudle KE, et al. Genet Med. 2017;19(2):215-223.

Standardization not completed for all known pharmacogenes or consensus not reached

Additional standardization opportunities exist beyond the genes presented here. For example, *VKORC1* is the one CPIC level A gene (https://cpicpgx.org/genes-drugs) on which we did not reach a consensus. This gene is tested primarily in the context of predicting starting doses of the common anticoagulant warfarin, which is also dependent on *CYP2C9*. Therefore, many laboratories report a drug-centered phenotype such as "greatly increased sensitivity to warfarin" (see the CPIC guideline for warfarin[21]), which complicated standardization of *VKORC1* terms following the formats used for other genes. In addition, *VKORC1* genotype and inferred phenotypes for warfarin dosing are also reported by some laboratories and the CAP proficiency testing surveys according to the *CYP2C9* and *VKORC1* policy statement published by the ACMG in 2008,[22] which further could have added to the difficulty in standardizing *VKORC1*.

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Example: current terms for *VKORC1* in ClinVar

	Variation *Location*	Gene(s)	Condition(s)	Clinical significance (Last reviewed)	Review status
6.	NM_024006.5(**VKORC1**):c.*245G>A *GRCh37:* Chr16:31102210 *GRCh38:* Chr16:31090889	**VKORC1**	Vitamin K-Dependent Clotting Factors	Uncertain significance (Jun 14, 2016)	criteria provided, single submitter
7.	NM_024006.5(**VKORC1**):c.*145T>C *GRCh37:* Chr16:31102310 *GRCh38:* Chr16:31090989	**VKORC1**	Vitamin K-Dependent Clotting Factors	Uncertain significance (Jun 14, 2016)	criteria provided, single submitter
8.	NM_024006.5(**VKORC1**):c.*134G>A *GRCh37:* Chr16:31102321 *GRCh38:* Chr16:31091000	**VKORC1**	acenocoumarol response - Dosage, phenprocoumon response - Dosage, warfarin response - Dosage, Vitamin K-Dependent Clotting Factors	drug response (Dec 11, 2017)	reviewed by expert panel
9.	NM_024006.5(**VKORC1**):c.383T>G (p.Leu128Arg) *GRCh37:* Chr16:31102564 *GRCh38:* Chr16:31091243	**VKORC1**	Warfarin response	drug response (Aug 14, 2017)	no assertion criteria provided
10.	NM_024006.5(**VKORC1**):c.358C>T (p.Leu120=) *GRCh37:* Chr16:31102589 *GRCh38:* Chr16:31091268	**VKORC1**	Vitamin K-Dependent Clotting Factors	Likely benign (Jun 14, 2016)	criteria provided, single submitter

Example: current terms for *mt-RNR1* in ClinVar

	Variation *Location*	Gene(s)	Condition(s)	Clinical significance (Last reviewed)	Review status
☐ 1.	NC_012920.1:m.750A>G *GRCh37:* ChrMT:750 *GRCh38:* ChrMT:750	MT-RNR1	not provided	not provided	no assertion provided
☐ 2.	m.827A>G *GRCh37:* ChrMT:827 *GRCh38:* ChrMT:827	MT-RNR1	Aminoglycoside-induced deafness, Deafness, nonsyndromic sensorineural, mitochondrial, Gentamicin response	drug response (Aug 1, 2018)	criteria provided, single submitter
☐ 3.	NC_012920.1:m.869C>T *GRCh37:* ChrMT:869 *GRCh38:* ChrMT:869	MT-RNR1	not provided	Likely benign (May 10, 2016)	criteria provided, single submitter
☐ 4.	m.951G>A *GRCh37:* ChrMT:951 *GRCh38:* ChrMT:951	MT-RNR1	not specified	Likely benign (Apr 13, 2017)	criteria provided, single submitter
☐ 5.	NC_012920.1:m.953T>C *GRCh37:* ChrMT:953 *GRCh38:* ChrMT:953	MT-RNR1	not specified	Likely benign (Mar 2, 2017)	criteria provided, single submitter
☐ 6.	NC_012920.1:m.954C>T *GRCh37:* ChrMT:954 *GRCh38:* ChrMT:954	MT-RNR1	not specified	Benign (Nov 27, 2017)	criteria provided, single submitter
☐ 7.	m.956C>T *GRCh37:* ChrMT:956 *GRCh38:* ChrMT:956	MT-RNR1	not specified	Uncertain significance (Jan 8, 2013)	criteria provided, single submitter

Terms used for clinical significance in ClinVar

Clinical significance value	Guidance for use in ClinVar SCV records
Benign	Asrecommended by ACMG/AMPfor variants interpreted for Mendelian disorders.
Likely benign	Asrecommended by ACMG/AMPfor variants interpreted for Mendelian disorders.
Uncertain significance	Asrecommended by ACMG/AMPfor variants interpreted for Mendelian disorders.
Likely pathogenic	Asrecommended by ACMG/AMPfor variants interpreted for Mendelian disorders.
Pathogenic	Asrecommended by ACMG/AMPfor variants interpreted for Mendelian disorders. Variants that have low penetrance may be submitted as "Pathogenic"; please also include information about the penetrance in a "Comment on clinical significance".
drug response	A general term for a variant that affects a drug response, not a disease. We anticipate adding more specific drug response terms based on arecommendation by CPIC.
association	For variants identified in a GWAS study and further interpreted for their clinical significance.
risk factor	For variants that are interpreted not to cause a disorder but to increase the risk.
protective	For variants that decrease the risk of a disorder, including infections.
Affects	For variants that cause a non-disease phenotype, such as lactose intolerance.
conflicting data from submitters	Only for submissions from a consortium, where groups within the consortium have conflicting intepr
other	If ClinVar does not have the appropriate term for your submission, we ask that you submit "other" as clinical significance and contact us to discuss if there are other terms we should add.
not provided	For submissions without an interpretation of clinical significance. The primary goal of ClinVar is to archive reports of clinical significance of variants. Therefore submissions with a clinical significance of "not provided" should be limited to: • "literature only" submissions that report a publication about the variant, without interpreting the clinical significance • "research" submissions that provide functional significance (e.g. undetectable protein level) but no interpretation of clinical significance • "clinical testing" or "phenotyping only" submissions from clinics or physicians that provide additional information about individuals with the variant, such as observed phenotypes, but do not interpret the clinical significance

Additional standardized terms will be needed that are beyond the scope of previous term standardization effort

Identifying genes for term standardization

- Inclusion:
  - CPIC level A or B genes
  - Currently being considered for guidelines per Kelly Caudle
    - *COMT* (level C)
    - *OPRM1* (level C/D)
  - Currently being considered for implementation
    - *F5* (level C)
- Exclusion
  - Standardized in Part 1
    - Drug metabolizing enzyme
      - E.g. *NAT*, *CYP4F2*
    - Drug transporter
      - E.g. *ABCB1*
- When drug-gene pairs with similar relationships were identified, one can be kept as a representative
  - E.g. Valproic acid and urea cycle enzymes, *RYR1/CACNA1S* and malignant hyperthermia
  - Enzyme deficiencies treated by drug
    - *GBA* and valaglucerase alfa, *NAGS* and carglumic acid

Genes with CPIC guidelines with standardized terms

Gene	Drug	CPIC Level	Efficacy, adverse reaction, both?	Description
TPMT/NUDT15	thiopurines	A	both efficacy and adverse reaction	PK basis
CYP2C19	clopidogrel, voriconazole, PPIs, antidepressants	A	both efficacy and adverse reaction	PK basis
CYP2C9	warfarin, NSAIDs, phenytoin	A	both efficacy and adverse reaction	PK basis
CYP2D6	codeine, antidepressants, atomoxetine	A	both efficacy and adverse reaction	PK basis
HLA	abacavir, allopurinol, carbamazepine, oxcarbazepine	A	adverse reaction only	immune risk
SLCO1B1	simvastatin	A	adverse reaction only	PK basis
DPYD	fluoropyrimidines	A	adverse reaction only	PK basis
CYP3A5	tacrolimus	A	both efficacy and adverse reaction	PK basis
UGT1A1	atazanavir	A	adverse reaction only	PK basis

Most are PK basis

Non-standardized genes with CPIC guidelines

Gene	Drug	CPIC Level	Efficacy, adverse reaction, both?	Description
RYR1/CACNA1S	halogenated anesthetics, succinylcholine	A	Adverse reaction only	Variants in Ca channels cause adverse drug reaction
CFTR	ivacaftor	A	Efficacy only	Loss of function variants predict drug efficacy (drug targets specific Cl channel variants)
G6PD	rasburicase	A	Adverse reaction only	Variants cause adverse drug reaction through loss of drug detoxification pathway
IFNL3	peginterferon alfa-2a	A	Efficacy only	Genotype predicts drug efficacy
VKORC1	warfarin	A	Both efficacy and adverse reaction	Variants cause altered efficacy and adverse reaction risk due to dose sensitivity

Non-standardized genes without CPIC guidelines that may be considered in the future

Gene	Drugs	CPIC Level	Efficacy, adverse reaction, both?	Description
MT-RNR1	aminoglycoside antibacterials	A/B	Adverse reaction only	Mitochondrial rRNA variants cause ototoxicity
Enzyme deficiencies *(GBA, NAGS)*	velaglucerase alfa, carglumic acid	B	Efficacy only	Velaglucerase alfa (VPRIV) treats GBA gene deficiency (Gaucher disease); Carglumic acid treats N-acetylglutamate synthase (NAGS) deficiency
HPRT1	mycophenolic acid	B	Adverse reaction only	MMF causes exacerbation of hereditary deficiency of HPRT1 leading to accumulation of uric acid
ABL2, ASL, ASS1, CPS1, OTC **(urea cycle enzymes)**	valproic acid	B	Adverse reaction only	Urea cycle enzyme deficiency. VPA causes hyperammonemic encephalopathy
POLG	valproic acid	B	Adverse reaction only	Mitochondrial DNA polymerase gamma. VPA causes acute liver failure with variant

Non-standardized genes without CPIC guidelines that may be considered in the future cont.

Gene	Drug	CPIC Level	Efficacy, adverse reaction, both?	Description
SCN1A	phenytoin, carbamazepine	B	?	Sodium channel modifying antiepileptic efficacy (& toxicity?) - drug site of action
SLC6A4	Citalopram, escitalopram	B/C	?	Serotonin transporter modifying SSRI efficacy (& toxicity?) - drug site of action
COMT	SSRI	C	?	Level C but considering now for guidelines. Enzyme metabolizing neurotransmitters
F5	eltrombopag, hormonal contraceptives	C	Adverse reaction only	Level C but considering now for implementation. Coagulation factor increasing risk of thrombosis.
OPRM1	opioids	C/D	?	Level C/D but considering now for guidelines. Opioid receptor- drug site of action

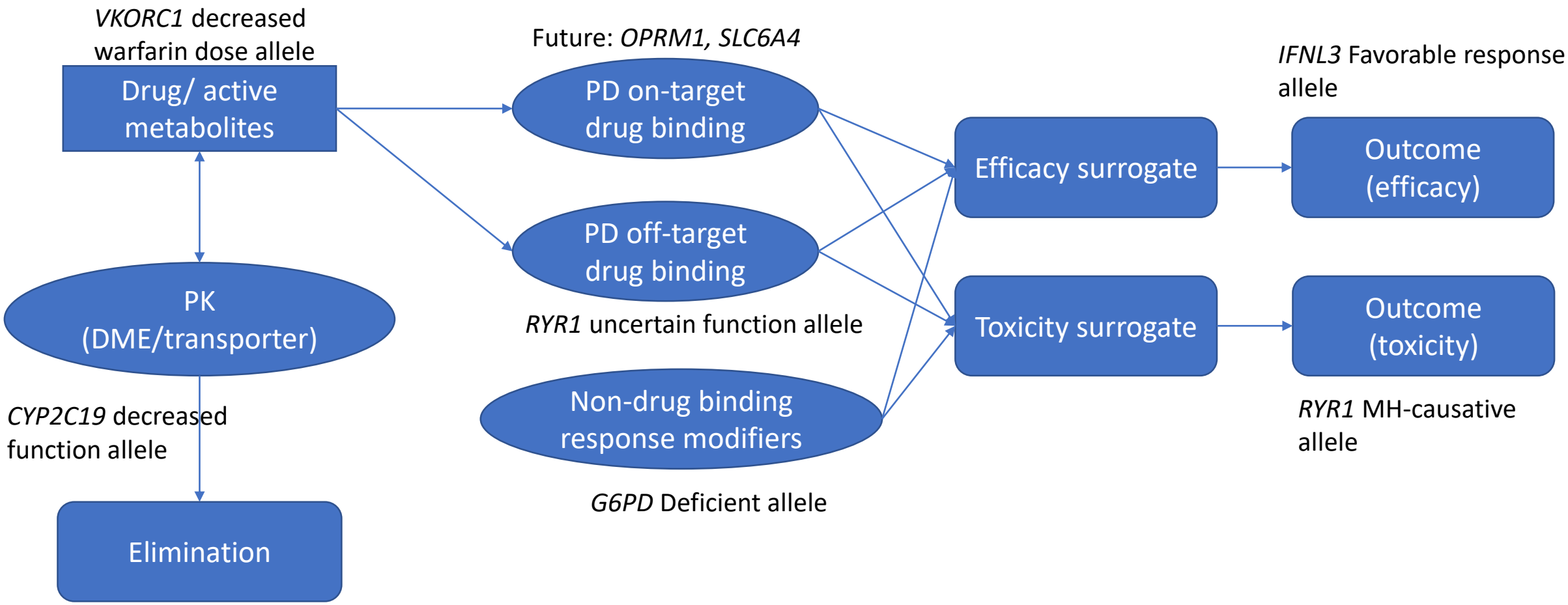
Allele function terms

Current CPIC allele functionality table (abbreviated) – *RYR1*

rsID	Nucleotide change	Protein change	Allele Functional Status	Finding	References
rs193922747	c.103T>C	p.C35R	Increased function	ositive IVCT	9066328, 16163667, 17710899, 20681998
				ncreased sensitivity to halothan ot increased sensitivity to caffe R2458H/C);	9334205
				ower maximal peak amplitudes r than with ildtype	9873004
rs63749869	c.14582G>A	p.R4861H	Uncertain function	-chloro-m-cresol resulted in alm s from control ndividuals or from an individual he absence of ny pharmacological activato sensitivity of he calcium release to	11741831
				utation detec	14985404
				ositive IV	12565913, 17081152
				ositive CHCT	23558838
rs118192170	c.14693T>C	p.I4898T	Decreased function	4898T led to a simultaneous incr n "leak" from he SR lumen; I4898T led to increased sensitivity to calcium but decreased binding of ryanodine vs. normal RYR1 and decreased response to caffeine, positive IVCT	10097181
				omozygous expression of I4897T in dyspedic myotubes results in a complete uncoupling of sarcolemmal excitation from voltage-gated SR Ca(2+) release without significantly altering esting cytosolic Ca(2+) levels, SR Ca(2+) content, or RyR1-mediated enhancement of dihydropyridine receptor (DHPR) channel activity; Coexpression of both I4897T and wild-type RyR1 esulted in a 60% reduction in voltage-gated SR Ca(2+) release, again without altering resting cytosolic Ca(2+) levels, SR Ca(2+) content, or DHPR channel activity	11274444
				ot elevated resting calcium; no spontaneous calcium oscillations; caffeine fails to activate calcium release	11524458
				ncorporation of the I4897T mutation into leaky release channels arising from either NH2-terminal (Y523S) or COOH-terminal (Y4795C) CCD mutations in RyR1 blocked the ability of hese mutations to cause store depletion and an elevation in resting calcium; myotubes expressing the double mutants were EC uncoupled since they completely lacked voltage-gated R calcium release	12642598
				o high-affinity 3H-ryanodine binding was detected; Ca2+ (pCa 7) and ATP (1 mM) present in the medium did not activate the variant channels as significantly as with wt RYR1; omotetrameric I4897T did not release Ca2+ at any of the Ca2+ concentrations tested; Ca2+-dependent Ca2+ release was not found in the CCD mutant I4897T; Expression of wt RyR with mutant RyR1 in the ratio 1:2 restored Ca2+ sensitivity partially for I4897T; expressed in the ratio 1:1, Ca2+ sensitivity was completely restored	15175001
				yotubes from the CCD pa-tients harboring the I4898T and R4893W RYR1 mutations showed a significant increase in the background levels of IL-6 released in the absence of an xogenous pharmacological activator of the RYR; background release of IL-6 blunted the stimulatory effect of 4-chloro-m-cresol to myo- tubes from the CCD patient harboring the 4898T mutation; addition of caffeine caused a significant increase in IL-6 release	15299003
				ositive IVCT in CCD patient	17081152
				YR1 mutant linked to CCD, I4898T, did not show any response at any concentration of 4-chloro-m-cresol including more than 500 M	20461000
				4-6-mo-old heterozygous Ryr1(I4895T/+) knock-in mice (IT/+) electrically evoked and 4-chloro-m-cresol-induced Ca(2+) release were significantly reduced and slowed in single intact exor digitorum brevis fibers; Single-channel measurements of purified recombinant channels incorporated in planar lipid bilayers revealed that Ca(2+) permeation was abolished for omotetrameric IT channels and significantly reduced for heterotetrameric WT:IT channels.	21149547
				nhibition of voltage-gated Ca(2+) release due to reduction in SR Ca2+ content	21825032
				ecreases voltage-gated calcium release and resting cytosolic calcium levels in mice; increases endoplasmic reticulum stress/unfolded protein response, enhances Ca2+ uptake/ROS roduction by interfibrillar mitochondria, activates proapoptotic pathways and decreases protein synthesis	28337975

- Current allele functional status describes RYR1 protein channel **biochemical** function, not **clinical** function.
- Increased, uncertain, and decreased function alleles are **all** high-risk MH-causative variants.

Allele terms have been used to describe different steps of the drug-PK-PD pathway



DME: drug-metabolizing enzyme; PD: pharmacodynamic

Non-standardized genes with CPIC guidelines

Gene	Drug	Gene product	Relation to drug	CPIC allele function term (table)	CPIC allele function term (guideline text, if different)	Example terms reported by labs*
RYR1/CACNA1S	halogenated anesthetics, succinylcholine	Channel	Variants in Ca channels cause adverse drug reaction	Increased, decreased, uncertain function	MH-causative allele; negative for MH-causative allele	High-risk (MH) allele; absence of specific high risk (MH) allele
CFTR	ivacaftor	Channel	Drug site of action; drug targets specific variants	-	Dysfunctional, non-functional	-
G6PD	rasburicase	Enzyme	Variants cause adverse drug reaction through loss of drug detoxification pathway	IV/normal; I-III/deficient	Nondeficient allele; deficient allele	Absence of G6PD deficient allele, G6PD deficient allele; pathogenic
IFNL3	peginterferon alfa-2a	Cytokine	Genotype predicts drug efficacy	-	Favorable response allele; Unfavorable response allele	-
VKORC1	warfarin	Enzyme	Variants cause altered efficacy and adverse reaction risk due to dose sensitivity	Decreased warfarin dose; normal	-	Functional

*from available sample reports: Mayo, Kailos, OneOme, PGxOne, Genesight, Northshore, ARUP, RPRD

Non-standardized genes without CPIC guidelines that may be considered in the future

Gene	Drug	Gene product	Relation to drug	Example terms reported by labs*
MT-RNR1	aminoglycoside antibacterials	Mitochondrial rRNA	Variants cause increased off-target binding leading to ototoxicity	High-risk variant, No high-risk variant detected (St. Jude)
Enzyme deficiencies *(GBA, NAGS)*	velaglucerase alfa, carglumic acid	Enzyme	Drugs replace deficient enzyme	-
HPRT1	mycophenolic acid	Enzyme	Drug causes exacerbation of enzyme deficiency and ADE	-
***ABL2, ASL, ASS1, CPS1, OTC* (urea cycle enzymes)**	valproic acid	Enzyme	Drug causes exacerbation of enzyme deficiency and ADE	-
POLG	valproic acid	Enzyme	Drug causes exacerbation of enzyme deficiency and ADE	-

*from available sample reports: Mayo, Kailos, OneOme, PGxOne, Genesight, Northshore, ARUP, RPRD

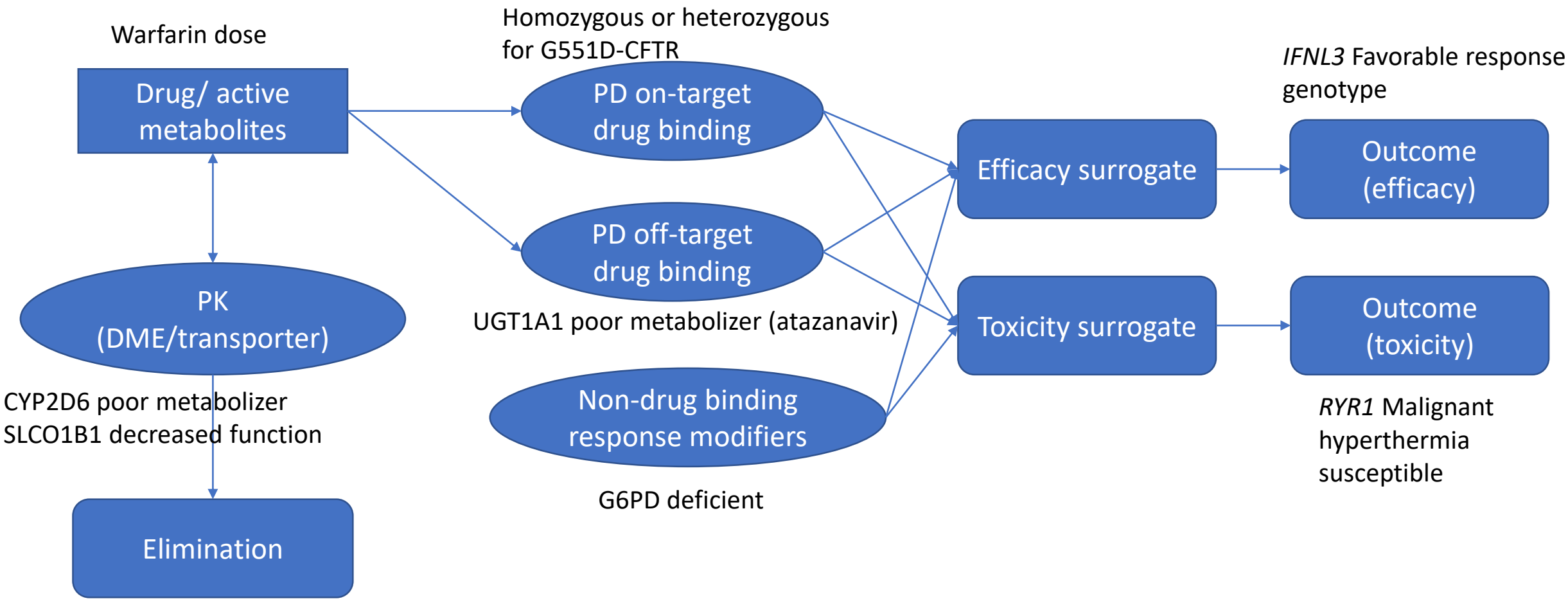
Non-standardized genes without CPIC guidelines that may be considered in the future cont.

Gene	Drug	Gene product	Relation to drug	Example terms reported by labs*
SCN1A	phenytoin, carbamazepine	Sodium channel	Site of action for sodium channel blocking antiepileptics	-
SLC6A4	citalopram, escitalopram	Serotonin transporter	Site of action for SSRIs	Decreased expression
COMT	SSRI	Enzyme	Enzyme alters concentrations of neurotransmitters also increased by drug	-
F5	eltrombopag, hormonal contraceptives	Coagulation factor	Further enhances risk of thrombosis with drugs	Factor V Leiden mutation
OPRM1	opioids	Receptor	Drug site of action	-

*from available sample reports: Mayo, Kailos, OneOme, PGxOne, Genesight, Northshore, ARUP, RPRD

Phenotype terms

Like allele function, phenotype terms have been used to describe different steps of the drug-PK-PD pathway



DME: drug-metabolizing enzyme; PD: pharmacodynamic

Non-standardized genes with CPIC guidelines

Gene	Drug	Gene product	Relation to drug	CPIC phenotype terms	Example terms reported by labs*
RYR1/CACNA1S	halogenated anesthetics, succinylcholine	Channel	Variants in Ca channels cause adverse drug reaction	Malignant Hyperthermia Susceptible; Uncertain MH Susceptibility	Increased risk; normal risk; negative
CFTR	ivacaftor	Channel	Drug site of action; drug targets specific variants	Homozygous/heterozygous/ noncarrier for G551D-CFTR; Homozygous for F508del-CFTR	Positive, Negative
G6PD	rasburicase	Enzyme	Variants cause adverse drug reaction through loss of drug detoxification pathway	Normal; variable; deficient; deficient with CNSHA	Normal G6PD Efficiency; Negative/Positive; Indeterminate; Pathogenic
IFNL3	peginterferon alfa-2a	Cytokine	Genotype predicts drug efficacy	Favorable/unfavorable response genotype	Increased/decreased sustained virologic response; reduced response; unfavorable response genotype; favorable/unfavorable genotype
VKORC1	warfarin	Enzyme	Variants cause altered efficacy and adverse reaction risk due to dose sensitivity	*VKORC1 c.-1639G>A A/G or A/A; VKORC1 c.-1639G>A G/G*	Resistant++, Resistant+, Normal, Sensitive-, Sensitive--; VKORC1 resistance, No VKORC1 resistance; Normal activity, Intermediate activity, Low activity Intermediate Warfarin Sensitivity; High sensitivity, Medium sensitivity, Low Sensitivity; rs9923231 A Allele Carrier; functional

*from available sample reports: Mayo, Kailos, OneOme, PGxOne, Genesight, Northshore, ARUP, RPRD

Non-standardized genes without CPIC guidelines that may be considered in the future

Gene	Drug	Gene product	Relation to drug	Example terms reported by labs*
MT-RNR1	aminoglycoside antibiotics	Mitochondrial rRNA	Variants cause increased off-target binding leading to ototoxicity	Aminoglycoside Ototoxicity Susceptible, Uncertain aminoglycoside ototoxicity (St. Jude) Positive, Negative
Enzyme deficiencies *(GBA, NAGS)*	velaglucerase alfa, carglumic acid	Enzyme	Drugs replace deficient enzyme	Positive, Negative; Pathogenic
HPRT1	mycophenolic acid	Enzyme	Drug causes exacerbation of enzyme deficiency and ADE	-
***ABL2, ASL, ASS1, CPS1, OTC* (urea cycle enzymes)**	valproic acid	Enzyme	Drug causes exacerbation of enzyme deficiency and ADE	Positive, Negative
POLG	valproic acid	Enzyme	Drug causes exacerbation of enzyme deficiency and ADE	-

*from available sample reports: Mayo, Kailos, OneOme, PGxOne, Genesight, Northshore, ARUP, RPRD

Non-standardized genes without CPIC guidelines that may be considered in the future cont.

Gene	Drug	Gene product	Relation to drug	Example terms reported by labs*
SCN1A	phenytoin, carbamazepine	Sodium channel	Site of action for sodium channel blocking antiepileptics	-
SLC6A4	citalopram, escitalopram	Serotonin transporter	Site of action for SSRIs	Long/short allele; Reduced/typical to increased expression; Reduced response HTTLPR Long Form Poor responder
COMT	SSRI	Enzyme	Enzyme alters concentrations of neurotransmitters also increased by drug	Poor/normal metabolizer; Intermediate/normal/high activity; Normal metabolizer; Non MET Homozygous
F5	eltrombopag, hormonal contraceptives	Coagulation factor	Further enhances risk of thrombosis with drugs	Normal risk, Increased risk; Non Factor V Leiden Carrier; Normal thrombosis risk; Negative
OPRM1	opioids	Receptor	Drug site of action	Reduced expressor; Asp/Asp isoform; rs1799971 A Allele Carrier/rs510679 TT genotype; Normal Opioid Responder; increased/decreased opioid sensitivity

*from available sample reports: Mayo, Kailos, OneOme, PGxOne, Genesight, Northshore, ARUP, RPRD

Conclusions

- Terms standardized in the original term standardization effort will not work universally for future pharmacodynamic pharmacogenes.
- Another Delphi process is likely necessary to standardize allele function terms and phenotype terms for non-standardized genes with CPIC guidelines already and other actionable genes.
- Heterogeneity in the pharmacodynamic genes presents unique challenges and considerations.

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Discussion