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

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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).

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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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RYR1 Allele Functionality Table

GENE: RYR1	8/16/2018					
	rsID[a]	Nucleotide change[b]	Protein change[c]	Allele Functional Status[d]	Finding	
	rs193922878	c.14512C>G	p.L4838V	Increased function	increased caffeine-induced calcium release in CHO cells	11928716
					accelatered CICR	11928716, 167
					associated with MH (supplemental material)	16917943
					positive IVCT; increased sensitivity to caffeine and chloro	19191329
	rs118192168				associated with MH (supplemental material)	16917943
					d to the left i	28403410
					n the homozy	16372898
						15731587, 214
						16163667, 193
	rs63749869	c.14582G>A	p.R4861H	Uncertain function[e]	4-chloro-m-cresol resulted in almost no increase in the [C	11741831
					mutation detected was concordant with CCD status only;	14985404
					positive IVCT in CCD patient	12565913, 170
					positive CHCT	23558838
	rs118192170	c.14693T>C	p.I4898T	Decreased function	I4898T led to a simultaneous increase in intracellular calc	10097181
					homozygous expression of I4897T in dyspedic myotubes r	11274444
					not elevated resting calcium; no spontaneous calcium osc	11524458
					incorporation of the I4897T mutation into leaky release ch	12642598
					no high-affinity 3H-ryanodine binding was detected; Ca2-	15175001
					myotubes from the CCD pa-tients harboring the I4898T an	15299003
					positive IVCT in CCD patient	17081152
					RYR1 mutant linked to CCD, I4898T, did not show any resp	20461000
					in 4-6-mo-old heterozygous Ryr1(I4895T/+) knock-in mice	21149547
					Inhibition of voltage-gated Ca(2+) release due to reductio	21825032
					decreases voltage-gated calcium release and resting cyto	28337975

Term Standardization II

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

- In addition to these genes with CPIC guidelines, there are also genes without CPIC guidelines but are CPIC level A, B, or C genes that may need to be considered in the future
  - *GBA*, *NAGS*, *HPRT1*, *POLG*, *COMT*, *OPRM1*, *SCN1A*, *SLC6A4*, *F5* and urea cycle enzymes (*ABL2*, *ASL*, *ASS1*, *CPS1*, and *OTC*).

- **Assessment**
  - Define terms that need to be evaluated and standardized. (see text above for assessment)
- **Development**
  - Create a list of options for terms (literature review and survey to genetic testing labs)
- **Prioritization**
  - Delphi 1: Experts will specify their level of agreement or disagreement on a symmetric agree-disagree scale (1-4) for each set of gene terms. Experts can also list additional terms.
- **Refinement:**
  - Delphi 2: For each gene, retain terms in which 70% of the experts agreed or strongly agreed in Delphi 1*.
  - Experts will pick 1 set of terms per gene/gene group.
  - Results from prior survey will be made available to the experts.
- **Consensus**
  - Delphi 3-?: For each gene/gene group, retain top terms selected by experts.
  - Repeat process until 70% consensus for one set of terms/gene is achieved. Results from prior survey will be made available to the experts.
- **Validation**
  - After 70% consensus reached, terms will be circulated to the experts again for final review and feedback.

Seeking experts

- Clinicians (pharmacists, physicians, nurses, genetic counselors, etc) with a working knowledge of pharmacogenetics.
- Researchers with at least 2 years of PGx research experience
- Clinical laboratory scientist or staff with at least 2 years of PGx experience
- Genomics experts
- PGx implementers
- EHR standards experts/medical informatics (PGx experience not required but involvement in HL7 or similar experience preferred)
- Gene specific experts for genes included in this project (i.e. *RYR1*, *CACNA1S*, *CFTR*, *G6PD*, *IFNL3*, *mtRNR1 GBA*, *NAGS*, *HPRT1*, *POLG*, *COMT*, *OPRM1*, *SCN1A*, *SLC6A4*, *F5, ABL2*, *ASL*, *ASS1*, *CPS1*, and *OTC*)
- CPIC guideline authors
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PharmGKB

CPIC™ Clinical Pharmacogenetics Implementation Consortium

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