Official journal of the American College of Medical Genetics and Genomics **ORIGINAL RESEARCH ARTICLE** | Genetics inMedicine

Open

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

Kelly E. Caudle, PharmD, PhD[1], Henry M. Dunnenberger, PharmD[2], Robert R. Freimuth, PhD[3], Josh F. Peterson, MD[4,5], Jonathan D. Burlison, PhD[1], Michelle Whirl-Carrillo, PhD[6], Stuart A. Scott, PhD[7], Heidi L. Rehm, PhD[8], Marc S. Williams, MD[9], Teri E. Klein, PhD[6], Mary V. Relling, PharmD[1], James M. Hoffman, PharmD, MS[1]

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.

Genet Med advance online publication 21 July 2016

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

Request SNOMED codes be standardized to CPIC phenotype terms

TPMT – SNOMED CT Code
Thiopurine methyltransferase deficiency

vs

TPMT- standardized Terms
TPMT - Normal Metabolizer (normal dose)
TPMT - Intermediate Metabolizer (60% dose)
TPMT - Poor Metabolizer (5% dose)

SNOMED Submission:
Work Completed by CPIC Informatics

- Defined scope of submission to include these genes:
  - CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, TPMT, UGT1A1, HLA-B (15:02, 57:01, 58:01), HLA-A (31:01)
- Reviewed existing SNOMED pharmacogenetic terms
  - Found substantial variability in both terms and location in tree structure

SNOMED Submission:
Work Completed by CPIC Informatics

- Proposed tree structure position for new phenotype terms
- Submission process
  - Reviewed submission procedures
  - Determined we must make a unique submission for each gene
  - Started drafting submission

Proposed SNOMED Tree Structure

- SNOMED CT Concept → Clinical finding → Evaluation finding → Genetic finding → Pharmacogenetic phenotype → PHENOTYPE TERM (e.g., CYP2D6 intermediate metabolizer)

- Contrast to existing terms and tree structure
  - Actionable phenotypes often listed as diseases or disorders
  - Others as enzyme or laboratory test
  - Range of location in tree structure; some very deep (e.g. CYP2D6)

Concept: [422510002] Extensive metabolizer due to cytochrome p450 CYP2D6 variant

UMLS information

CUI: [C1827317] Extensive metabolizer due to cytochrome p450 CYP2D6 variant

Semantic Types:Disease or Syndrome [T047]

Concept Status	Definition Status
Active	Primitive

Descriptions (3)

Id	Description
2640305019	Extensive metabolizer due to cytochrome p450 CYP2D6 variant (disorder)
2644360015	Extensive metabolizer due to cytochrome p450 CYP2D6 variant
2648320012	Extensive metabolizer due to CYP2D6

Parents (1)

Relationships from *this* concept (1)

Tree Positions (1)

Extensive metabolizer due to cytochrome p450 CYP2D6 variant

SNOMED CT Concept

Clinical finding

Disease

Metabolic disease

Enzymopathy

Disorder due to cytochrome p450 enzyme variant

Disorder due cytochrome p450 CYP2D6 variant

Next Steps for SNOMED Submission

- Conduct BRIEF survey to confirm CPIC Informatics Plan
  - About 5 questions plus a few demographic questions
  - Send to CPIC members with the minutes from this call (next week)
  - Post to PharmGKB to reach beyond CPIC membership
- Interested in responses from around the world since SNOMED is an international terminology
- If survey shows consensus, expect to submit by June 1

Questions and Discussion

Final Standardized Terms: Allele function

Term/Gene Category	Final Term	Functional Definition	Example diplotypes/alleles
Allele Functional Status-all genes	Increased Function	Function greater than normal function	*CYP2C19*17*
	Normal Function	Fully functional/wild-type	*CYP2C19*1*
	Decreased Function	Function less than normal function	*CYP2C19*9*
	No Function	Non-functional	*CYP2C19*2*
	Unknown Function	No literature describing function or the allele is novel	*CYP2C19*29*
	Uncertain Function	Literature supporting function is conflicting or weak	*CYP2C19*12*

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

Final Standardized Terms: Phenotype for Drug Metabolizing Enzymes

For example: *CYP2C19, CYP2D6, CYP3A5, CYP2C9, TPMT, DPYD, UGT1A1*

Final Term	Functional Definition	Example diplotypes/alleles	Term/Gene Category
Ultra-rapid 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 ultra-rapid 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*

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

Final Standardized Terms: Phenotype for Drug Transporters

For example: *SLCO1B1*

Final Term	Functional Definition	Example diplotypes/alleles	Term/Gene Category
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*

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

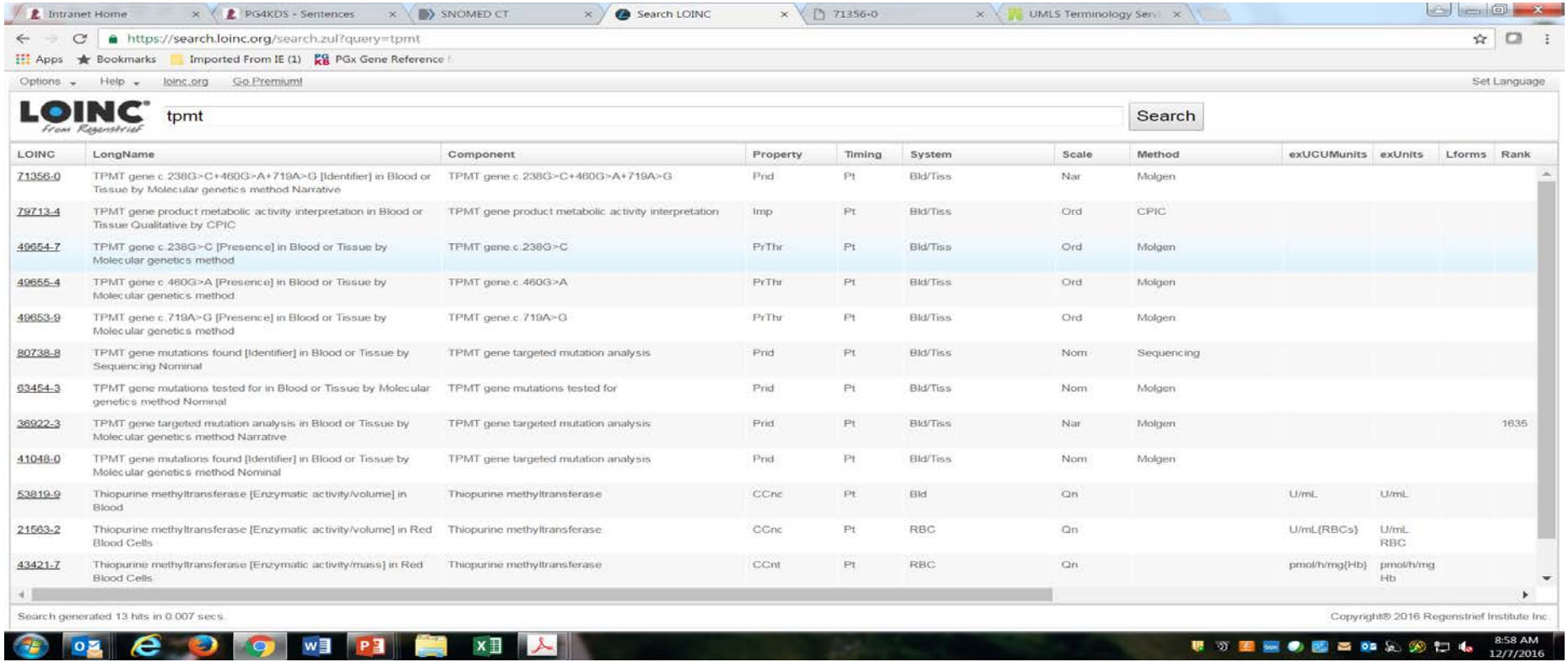
Final Standardized Terms: (HLA-genes) Phenotype for High-Risk Genotype Status

For example: *HLA-B*57:01*

Final Term	Functional Definition	Example diplotypes/alleles	Term/Gene Category
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	

Caudle KE, et al. *Genet Med.* 2016;Jul 21 [Epub ahead of print]

CPIC Informatics: working to standardize and clean up LOINC codes for all CPIC genes



LOINC	LongName	Component	Property	Timing	System	Scale	Method	exUCUMunits	exUnits	Lforms	Rank
71356-0	TPMT gene c.238G>C+460G>A+719A>G [Identifier] in Blood or Tissue by Molecular genetics method Narrative	TPMT gene.c.238G>C+460G>A+719A>G	Prid	Pt	Bld/Tiss	Nar	Molgen				
79713-4	TPMT gene product metabolic activity interpretation in Blood or Tissue Qualitative by CPIC	TPMT gene product metabolic activity interpretation	Imp	Pt	Bld/Tiss	Ord	CPIC				
49654-7	TPMT gene c.238G>C [Presence] in Blood or Tissue by Molecular genetics method	TPMT gene.c.238G>C	PrThr	Pt	Bld/Tiss	Ord	Molgen				
49655-4	TPMT gene c.460G>A [Presence] in Blood or Tissue by Molecular genetics method	TPMT gene.c.460G>A	PrThr	Pt	Bld/Tiss	Ord	Molgen				
49653-9	TPMT gene c.719A>G [Presence] in Blood or Tissue by Molecular genetics method	TPMT gene.c.719A>G	PrThr	Pt	Bld/Tiss	Ord	Molgen				
80738-8	TPMT gene mutations found [Identifier] in Blood or Tissue by Sequencing Nominal	TPMT gene targeted mutation analysis	Prid	Pt	Bld/Tiss	Nom	Sequencing				
63454-3	TPMT gene mutations tested for in Blood or Tissue by Molecular genetics method Nominal	TPMT gene mutations tested for	Prid	Pt	Bld/Tiss	Nom	Molgen				
36922-3	TPMT gene targeted mutation analysis in Blood or Tissue by Molecular genetics method Narrative	TPMT gene targeted mutation analysis	Prid	Pt	Bld/Tiss	Nar	Molgen				1635
41048-0	TPMT gene mutations found [Identifier] in Blood or Tissue by Molecular genetics method Nominal	TPMT gene targeted mutation analysis	Prid	Pt	Bld/Tiss	Nom	Molgen				
53819-9	Thiopurine methyltransferase [Enzymatic activity/volume] in Blood	Thiopurine methyltransferase	CCnc	Pt	Bld	Qn		U/mL	U/mL		
21563-2	Thiopurine methyltransferase [Enzymatic activity/volume] in Red Blood Cells	Thiopurine methyltransferase	CCnc	Pt	RBC	Qn		U/mL(RBCs)	U/mL RBC		
43421-7	Thiopurine methyltransferase [Enzymatic activity/mass] in Red Blood Cells	Thiopurine methyltransferase	CCnt	Pt	RBC	Qn		pmol/h/mg{Hb}	pmol/h/mg Hb		