CPIC terms Update

CPIC Call

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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

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Terminologies: Getting started with LOINC

- Necessary from laboratory perspective
- Relatively straightforward
  - CPIC connections (Bob Freimuth)
  - Interest from LOINC
- Not the entire solution
  - Clear in GIM paper

This project and recent work[13] have demonstrated that there is great diversity in how genetic test results are reported and interpreted,[23] which can lead to confusion among clinicians, patients, and researchers in the exchange and use of clinical genetic data. Clear opportunities exist to develop new terminologies and improve existing standards to represent genetic results and interpretations.[24] Although they do not represent comprehensive solutions, some progress has recently been made. An HL7 standard now exists that outlines how genetic test results could be reported.[25] The Logical Observation Identifier Names and Codes (LOINC) terminology, a widely used standard for reporting laboratory test results and interpretations,[26,27] is one terminology that could be used to report genetic interpretations, and it has recently been extended to support genetic data.[28] Therefore, to enable precise communication beyond the CPIC guidelines, encourage use of these terms within EHRs, and facilitate the implementation of pharmacogenetic CDS, we

LOINC complete before publication

obtained LOINC identifiers for pharmacogenetic interpretation codes and answer lists (**Supplementary Tables S4 and S5** online). Our work with LOINC has focused on standardizing pharmacogenetic test interpretation codes, and all the terms from the CPIC terminology-standardization project were registered as LOINC answer lists and were released on 21 December 2015 as part of LOINC 2.54.

SNOMED Use Case

- Health system wants to develop pharmacogenomic CDS
- Organizational standard is to use SNOMED codes to for custom CDS
- SNOMED codes are not sufficiently granular to send different messages per phenotype

Terminology Needs: For discussion

- Phenotype level? Or even more detail needed?
- Need to differentiate phenotype vs. activity testing?
- “Disease” or “Clinical finding”

Decisions from 11/21 CPIC Informatics Call

- Focus concepts on PHENOTYPE level
  - Other information (e.g. testing method) can be documented elsewhere)
- Activity testing/score is out of scope
  - Would be covered with phenotype and additional documentation; not covered in CPIC term standardization project

Decisions from 11/21 CPIC Informatics Call

- “Disease” vs. “Clinical Finding”
  - Consensus on clinical finding

Next Steps

- Move forward with drafting detailed proposal for all CPIC genes
- Review with CPIC Informatics
- Send to various groups for comment; suggestions discussed
  - Lab perspective (e.g. AMP)
  - HL7 Pharmacy Health IT Alliance (discussions started)
  - NAM DiGitize (continue to have call about every 2 months)

For Reference

CPIC Term Standardization Project

- Purpose:
  - To standardize phenotype terms in the CPIC guidelines and harmonize terms with external groups
    - Allele functional status terms
      - Low, absent, high, intermediate
    - Phenotype terms
      - UM, EM, IM, PM
- Groups surveyed:
  - Clinicians (physicians, pharmacists, nurses…)
  - Pharmacogenomics researchers
  - Genetic testing laboratory staff
  - Pharmacogenomics implementers
  - Clinical informatics

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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*

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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*

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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*

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

For example: SLCO1B1

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	

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SNOMED Analysis

- Entries for the following CPIC genes
  - CPY2C9, CYP2C19, CYP2D6, DPYD, G6PD, HLA-B, TPMT, UGT1A1, VKORC1
- Variation across genes
  - Level of detail in general
  - Place in SNOMED tree structure

SNOMED Analysis: Representative Genes

- CYP2C9
  - Multiple concepts exist
    - Cytochrome p450 CYP2C9 enzyme
    - Poor metabolizer due to cytochrome p450 CYP2C9 variant
    - Cytochrome p450 CYP2C9 enzyme deficiency
    - Disorder due to cytochrome p450 CYP2C9 variant
  - More complexity beyond concept

SNOMED Analysis: Representative Genes

- UGT1A1
  - Only one concept
  - Structure relatively straightforward
    - UGT1A1*28 polymorphism [Context 1] --> SNOMED CT Concept --> Clinical finding --> Evaluation finding --> Genetic finding --> Genetic polymorphism

SNOMED Analysis: Representative Genes

- HLA-B
  - Multiple concepts; one example:
    - “Human leukocyte antigen B 1502 antigen present”
  - Structure relatively straightforward
    - Human leukocyte antigen B 1502 antigen present --> SNOMED CT Concept --> Clinical finding --> Evaluation finding --> HLA antigen present

SNOMED Structure

- Do UGT1A1 and HLA-B represent model to follow?

- Further review of spreadsheet as needed

Terminology Needs: For discussion

- Phenotype level? Or even more detail needed?
- Need to differentiate phenotype vs. activity testing?
- Actual observation vs. “risk thereof”
- “Disease” or “Clinical finding”