

Term Standardization for Clinical Pharmacogenetic Test Results: alleles and phenotypes

Clinical Pharmacogenetics Implementation Consortium (CPIC)

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Background

Many different terms are used to describe allele function and assign clinical phenotype. For example, a genetic laboratory report might assign an individual carrying two non-functional *TPMT* alleles as either being “TPMT homozygous deficient” while another laboratory might use the term “TPMT no activity”. Also, these same laboratories might use different terminology to describe a similar phenotype for a different gene (e.g., an individual carrying two non-functional *DPYD* alleles might be described as “DPYD defective.”). This lack of standardization is often confusing to clinicians and patients as the actual phenotypes are the same (*i.e.* no function), but the terms describing the phenotypes are different and thus, might be interpreted differently. Moreover, the lack of standardization hinders the development of standardized approaches for reporting and sharing pharmacogenetic test results across laboratories and in electronic health records (EHRs). To maximize utility of pharmacogenetic test results and to fully implement CPIC guidelines, it is desirable to standardize these terms. Phenotype terms should also be easily interpreted by clinicians with basic pharmacogenetic training, and where possible, should be interchangeable across genes (e.g., the use of “TPMT deficient” and “DPYD deficient” to describe an individual carrying two non-functional alleles).

Project Purpose and Methods

The purpose of this project is to standardize terms in the CPIC guidelines that are used to characterize allele functional status and the presumed phenotype (generally based on diplotypes), and to encourage adoption by external groups (e.g., ClinGen, IOM’s roundtable on genomic medicine, EHR vendors, clinical laboratories etc.). Therefore, at the completion of this project all terms for Table 1 and Table 2 in the standard CPIC format will be standardized. Standardizing these terms will facilitate understanding each patient’s clinical phenotype for CPIC genes, and how that phenotype was determined from each patient’s genetic test results.

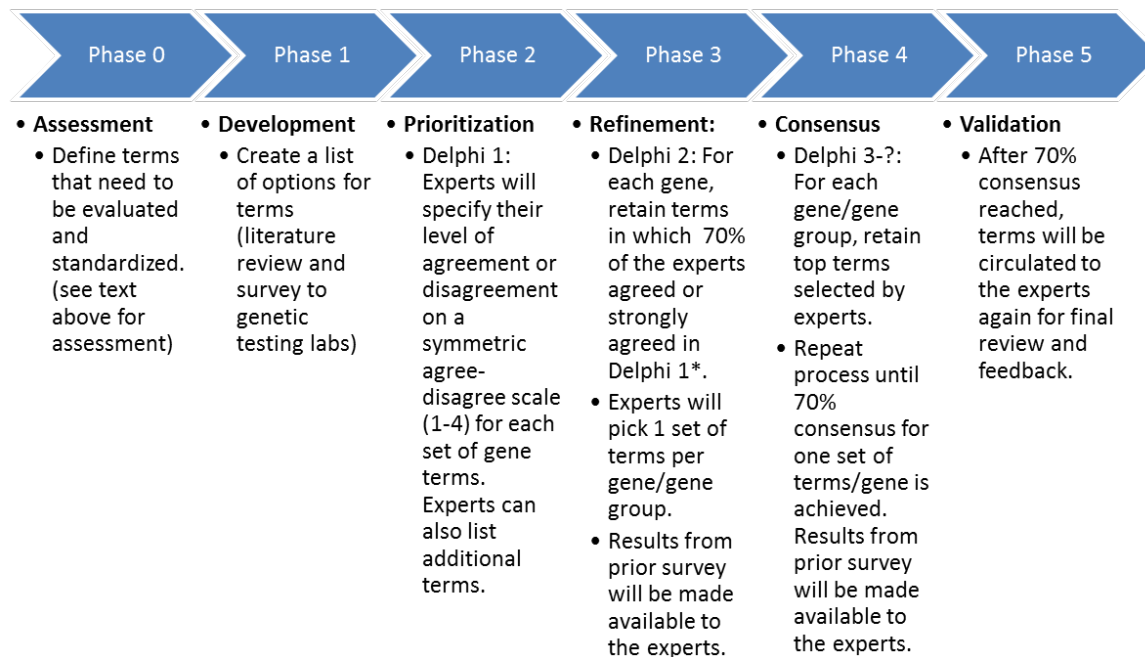
It may not be possible to standardize these terms across all genes, and therefore, as part of this project, genes may need to be grouped into categories according to their characteristics. For example, one approach may be needed for transporter genes and while another may be needed for CYP enzymes.

To create standardized terms, CPIC informatics has devised the following plan: ((1) review the literature and laboratory reports for genes in each of these groups and create a list of options for phenotype terms for CPIC genes; (2) using a modified Delphi method, survey experts, including the members of CPIC, ClinGen, CDC PGx working group, PGRN, and others to determine the best terms to use for each gene. Participation by experts outside of these groups will be solicited by posting an invitation to participate on PharmGKB. The modified Delphi method is a structured approach to determine consensus through iterative surveys of an expert panel (in this case the CPIC membership and others). Further details of the Delphi methods selected for this project are listed below. We expect at least 2 to 4 surveys of the CPIC membership, ClinGen’s PGx working group, IOM’s EHR Action Collaborative, and other experts will be

required to achieve consensus. 3) Adopt these terms in future CPIC guidelines and facilitate their adoption by external groups.

Modified Delphi Method

The modified Delphi method to reach consensus is summarized below. Experts who volunteer to participate in the consensus process will be asked to complete each survey. We will be using a modified Delphi approach as outlined by Hsu, et al. (1) If it becomes difficult to achieve consensus across the expert panel by the fourth survey, survey responses will be ranked and the Kendall's W statistic will be applied to facilitate final agreement.



*If experts select the same term for genes with similar characteristics (e.g. CYP enzymes), these genes will be grouped together for subsequent surveys.

Implications of this project for CPIC and Others

We expect that terms will provide a framework for each guideline author group to use. However, the authors will continue to be responsible for assigning alleles and diplotypes relationships to the terms.

While the purpose of this project is to standardize terms used in CPIC guidelines, we expect these terms to have broad implications for the implementation of pharmacogenomics. As standardized nomenclature becomes part of the CPIC guidelines, broader use of these terms will develop with other organizations (e.g. clinical laboratories, LOINC, HL7, etc.).

(1) Hsu, C.C. & Sandford, B.A. The Delphi Technique: Making Sense of Consensus. *Practical Assessment, Research and Evaluation* **12**, 1-8 (2007).