**Pharmacogenomics Consensus Group: OVERVIEW OF PHARMACOGENETIC VARIANT CURATION for Assigning Allele Clinical Function**

Using published evidence to link specific genes with specific drug effects has been undertaken by groups such as PharmGKB and CPIC (1-4). Some of the criteria (e.g. rarity of allele frequency in the population, familial segregation) used for assigning function to disease risk genes do not apply to pharmacogenes. Likewise, the terminology applied to disease risk variants (pathogenic, benign) do not apply to pharmacogenetic variants (5), which generally do not confer a phenotype unless the individual is challenged with an affected drug. For a subset of gene/drug pairs, consensus allele function terms have been developed (6) and assigned to specific pharmacogenetic alleles, and these assignments serve as part of the basis for clinical pharmacogenetic guidelines (7-27).

The purpose of this document is to describe the framework by which variants in pharmacogenes are assigned function, termed the “allele clinical functional status,” that can be used to determine which diplotypes drive potentially actionable prescribing decisions.

***A unique contribution of CPIC is to assign an allele function that leads to a phenotype assignment that can drive clinical prescribing actionability***. It is clear that there are cases for which a “biochemical” functional assignment can be made for an allele, but it does not completely correspond to clinical actionability (e.g. RYR1 alleles with increased and decreased activity both correspond to the same clinical recommendation of withholding inhaled anesthetics). Therefore, it is important to note that the primary goal of the CPIC guideline authorship committees is to assign an “Allele clinical functional status” as described in detail below. In this standard operation procedure (SOP) document we describe a process modified from that used by ClinGen for their gene-disease validity evaluation process (28). The purpose is to evaluate relevant clinical and experimental evidence supporting or contradicting a gene-drug relationship. As part of the CPIC guideline development process, allele functions are assigned based on clinical expertise of appropriate gene and drug experts (i.e. guideline authors).

# Assignment of Allele Clinical Function Status versus Allele BIOCHEMICAL Function Status

**Allele Clinical Function Status:** The goal is to assign “Allele Clinical Function Status” to pharmacogenetic allelic variants (i.e. haplotypes) using a standardized procedure and standardized terms. Allele clinical function assignments should be informed by the likelihood that for most pharmacogenes, it is the diplotype (and the inferred phenotype) that will drive clinical actionability. This differs from many disease-risk genes or HLA high-risk variants, where the presence of a single high-risk variant (even if mono-allelic) is actionable. Therefore, experts are encouraged to consider the consequence of the variant allele when combined with another allele in a diplotype, and the different phenotypic groupings likely to be needed for the gene (using the standardized terms) that will drive prescribing actions. Experts will review published and publicly available evidence, and assign an Allele Clinical Function Status to each allele (along with an optional assessment on strength of evidence), or indicate that such an assignment is not yet possible based on the evidence (see below, Evidence Review and Table).

CPIC Allele Clinical Function Status may be used to generate lists of which alleles or variants of a gene may be clinically actionable. Clinically actionable means that if a variant is present in the right gene dosage (e.g. homozygosity, in compound heterozygosity with another actionable variant, or combined with a normal function allele for a gene for which haploinsufficiency is actionable), prescribing decisions will be altered from normal (i.e. standard starting dose) prescribing actions. The decision as to how each pharmacogene must be minimally interrogated to adequately rule in or out actionable variants is a complex task, and beyond the scope of this document. Other groups, such as Association for Molecular Pathology (AMP), have taken on the task of developing recommendations for minimum standards for clinical pharmacogenetic genotyping (29, 30).

**Allele biochemical function status (not clinically actionable):** Expert panels have the option of assigning “Allele biochemical function status” (not allele clinical function status) to alleles. This is to accommodate their evaluation of data on allele function that are of scientific interest, but which do NOT rise to a level supporting clinical actionability. This is a separate designation from the mandatory CPIC “Allele Clinical Function Status” which is to be used to translate diplotypes into phenotypes and prescribing actionability. Thus, allele biochemical status will NOT be used for purposes of deciding on actionability of alleles in CPIC guidelines.

**Allele Clinical Function Substrate Specificity:** Although there are sometimes data suggesting that the function of a particular allelic variant may be substrate-specific, i.e. may vary from one substrate to another, the CPIC Allele Definition, Allele Functionality, and Diplotype-to-Phenotype tables are constructed to reflect function towards the majority of substrates (i.e. based on the field “Allele Clinical Function Status”). The CPIC allele function table, however, will allow for indicating which alleles have “strong” substrate-specific effects toward specific drugs. “Strong” substrate specific effects are those that would change the allele functional assignment (e.g., normal vs decreased function or decreased vs no function) such that the resulting phenotype would change prescribing from the default. This should be rare but may occur. Substrate specificity will be referenced in the CPIC guidelines for drugs that are affected, likely resulting in drug-specific tables for prescribing recommendations for that gene/drug pair.

Inclusion of variants/alleles and evidence review

**Inclusion of Variants/Alleles:** Evidence should be summarized on a variant, or an allele, if there are peer-reviewed publications on the function or the clinical actionability of the variant or allele, and in some cases, if clinical labs are already routinely testing for the variant or allele (even if function is uncertain or unknown). Whenever available, allele definitions will match those in PharmVar or other legacy gene authorities (e.g. TPMT Allele Nomenclature Committee, UGT Official Nomenclature). Guideline authors may nominate alleles for inclusion based on their expert knowledge of the gene and possible actionability.

**Evidence Review:** The evidence is collected primarily from published peer-reviewed literature but may also be retrieved from publicly accessible curated resources, such as variant databases including ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), PharmVar (https://www.pharmvar.org/), and PharmGKB (https://www.pharmgkb.org/), which can be used with discretion and if their variant curation process is approved by the guideline gene experts. Literature searches will be conducted using PubMed (<http://www.ncbi.nlm.nih.gov/pubmed)>and/or Google Scholar (<http://scholar.google.com/)>(which has a full-text search feature). The expertise of the guideline authorship committee will be leveraged to refine and describe the procedure used for literature review, to ensure that no critical publications are overlooked.

For well-established associations, a comprehensive review of all available evidence may not be required for some allelic variants. The authors may focus on curating and evaluating relevant evidence for more recently-discovered alleles, alleles for which new information has become available and/or those with conflicting data.

**Classifying different evidence types used to assign Allele Clinical Function:** The evidence will be classified as to the type of evidence supporting the functional assignment (e.g. whether it stems from well-controlled clinical studies, meta-analyses of multiple well controlled clinical studies, small case series, case reports, preclinical *in vivo* studies, preclinical *in vitro* studies, or is solely based on computational predictions of function) (5, 28). *In silico* predictions may be considered, particularly if the sequence change predicts consequences such as a premature stop codon that will likely cause termination of translation (5). The authors can choose to organize the assignment of strength of evidence based on individual findings (which might have supportive and conflicting citations), or to assign the strength of evidence in single citations, or both. Regardless, the authors must assign an Allele Clinical Function to each allele, based on the totality of the available evidence. Authors should consider the likely impact of allele clinical function assignment on the downstream diplotype and phenotype, and the impact on prescribing implications that are based on the resulting phenotype. Authors should decide if they would change prescribing based on the presence of this allele. If so, then the allele should be assigned a Clinical Function, even if the evidence is weak.

In the case of insufficient or conflicting evidence, the variant will be assigned an Allele Clinical Function of “uncertain function” (see table below). Alleles will be assigned “unknown function” if no evidence regarding their functional status can be found during the literature review process. A guideline will not provide a recommendation for diplotypes composed of two “uncertain function” or “unknown function” alleles or a combination thereof. For some genes, an individual carrying one “uncertain function” or “unknown function” allele in combination with a known function actionable allele (i.e. increased, decreased, or no function) will result in assignment of a “possible” phenotype to these individuals, so that prescribers are alerted that an abnormal phenotype is possible. Additional drug-specific actionability an apply to these “possibly” high-risk phenotype on a guideline-specific basis. For example, for *TPMT,*  an individual carrying one no-function allele plus one uncertain function allele would be assigned a “possible” intermediate metabolizer phenotype, which is actionable, rather than designate the individual as “uncertain” phenotype, because the evidence is so strong that the presence of at least one no-function allele confers a haplo-insufficient phenotype and requires a dosage decrease of the thiopurine.

**Strength of Evidence:** The Strength of Evidence assignment relates to the evidence that supports the Allele Clinical Function Status (not the Allele Biochemical Function Status) (see Table).

**Table: Assignment of Allele Clinical Function.** Summary of the evidence required to assign increased, normal, decreased or no function opposed to an allele opposed to “uncertain function”. The process is modified from that used by ClinGen for their gene-disease validity evaluation process (28). Allele function is assigned using CPIC standardized terms when possible.

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| --- | --- | --- |
| **Supportive Evidence needed to assign function vs uncertain** | **DEFINITIVE** | The causal role of this allelic variant in this particular drug phenotype has been repeatedly demonstrated, and has been upheld over time (in general, at least 3 years). No convincing evidence has emerged that contradicts the role of the allele in the specified drug phenotype. |
|  |  |
| **STRONG** | The causal role of this allelic variant in the drug phenotype has been independently demonstrated in at least two separate clinical studies providing **strong** supporting evidence for this allele’s role in drug phenotype; there is compelling variant-level evidence from different types of supporting experimental data. In addition, no convincing evidence has emerged that contradicts the role of the allele in the noted drug phenotype. |
|  |  |
| **MODERATE** | There is **moderate** evidence to support a causal role for this variant in this drug phenotype, including both of the following types of evidence:   * At least 2 patient cases demonstrated drug phenotype causality * Some *in vitro* experimental data (e.g. engineered variant and effect measures support the variant-drug phenotype association)   AND no convincing evidence has emerged that contradicts the role of the variant in the noted drug phenotype. |
|  |  |
| **LIMITED** | There is **limited** evidence to support a causal role for this allelic variant in this drug phenotype, including at least one patient case and at least one of the following types of evidence:   * Limited *in vitro* data (e.g. correlative data) support the variant-drug phenotype association * Computational activity predictions overall support *in vivo* and/or *in vitro* data (5)   AND no convincing evidence has emerged that contradicts the role of the  variant in the noted drug phenotype. |
|  | LIMITED: IN VITRO ONLY | The only evidence to support a causal role for this allelic variant in this drug phenotype is in vitro or computational; no case of altered drug disposition or effect are reported.  • In vitro data (experimental or correlative data) support the variant-drug phenotype association  • Computational activity predictions strongly support the in vitro data (5)  AND no convincing evidence has emerged that contradicts the role of the variant in the noted drug phenotype.  Function assignment based on in limited in vitro data only should only be made for genes whose resulting drug phenotype could result in life-threatening consequences if not considered. In most cases, alleles with only in vitro data should be assigned UNCERTAIN clinical allele function. |
|  | |  |
| **Inadequate EVIDENCE = uncertain function** | | Fewer than 2 patient cases with no convincing *in vitro* experimental data, with extremely limited or conflicting *in vitro* data.  This designation should be used when the evidence is not sufficiently strong to support a clinical functional status that can inform prescribing actionability. The threshold for what evidence is sufficient to inform actionability may differ among genes. |
| **No EVIDENCE = unknown function** | | There is no literature describing function |

Notes on conflicting evidence.

1. Many clinical studies reporting the lack of an association between a variant and a phenotype are underpowered. Such studies must be down-weighted when considering them, such that some low-power studies may not be considered “conflicting” at all.
2. In some cases, both supporting and conflicting data may be equally convincing. The authors will weigh the clinical importance of a type I error (acting on a variant which may not have been actionable) vs a type II error (not acting on a variant which should have been actionable).
3. For these reasons, CPIC Allele Clinical Function may differ from non-clinical functional assignments.
4. Alleles for which the evidence is not sufficient to support clinical actionability (i.e. a prescriber will not act if this allele is present in the correct gene dosage) are categorized as “uncertain function”. Such alleles are periodically re-assessed and may be re-classified as more evidence becomes available.

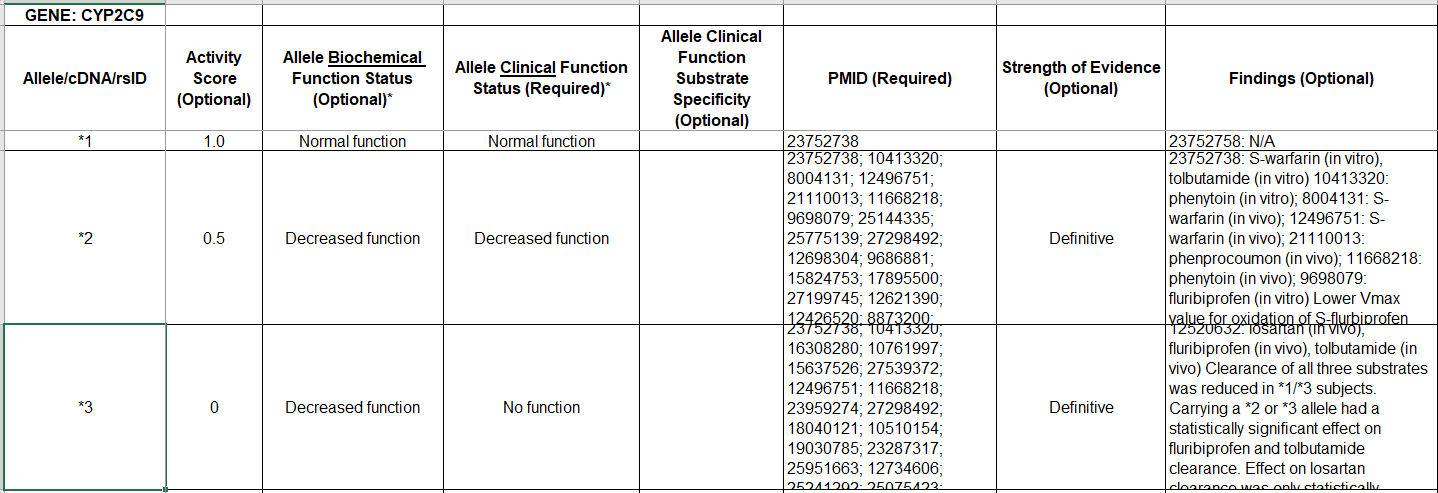
Summary Matrix for functional assignment to alleles

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Term/Gene Category** | **Allele functional Term** | **Functional Definition** | **Considerations for diplotype/phenotype that may inform the assignment of function to an allele** | **Example** |
| Allele Clinical Functional Status-pharmaco genes based on enzymes, transporters, or gene products with known quantitative effects | Increased Function | Function greater than normal function | When both alleles have increased function, the phenotype of the patient is considerably higher than a normal metabolizer warranting different categorization (e.g. “ultrarapid metabolizer”). There are some genes (e.g. *TPMT, UGT1A1*) for which the “normal metabolizer” phenotype encompasses both normal and very rapid metabolism, particularly when no drugs are known to require dosage adjustments compared to normal metabolizers | *CYP2C19\*17*  *CYP2D6\*2x2* |
| Normal Function | Fully functional | When both alleles have normal function, the phenotype of the patient is “normal metabolizer.” | *CYP2C19\*1*  *CYP2D6\*1* |
| Decreased Function | Function less than normal function but greater than no function | When patients are homozygous for decreased function alleles, or when patients have one decreased function allele and one normal function or no function allele, the phenotype of such a person is different compared to a patient who is homozygous for a normal function or homozygous for a no function allele | *CYP2C19\*9*  *CYP2D6\*10* |
| No Function | Non-functional | When both alleles have no function, the phenotype of the patient is “poor metabolizer”. The patient with this phenotype may have no metabolic activity or very low activity. Many “no function” alleles have some residual activity. Patients with one “no function” allele and one “normal function” allele, are intermediate metabolizers. | *CYP2C19\*2*  *CYP2D6\*4* |
| Unknown Function | No literature describing function, or the allele is novel | N/A | *CYP2C19\*29*  *CYP2D6\*58* |
| Uncertain Function | Literature supporting function is insufficient, conflicting or weak | N/A | *CYP2C19\*12*  *CYP2D6\*22* |
| Allele Functional status for high-risk genes with unclear mechanism (*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 |  |
| \*All terms should begin with the gene name (e.g., CYP2D6 Poor metabolizer, TPMT Normal metabolizer, SLCO1B1 Decreased Function) | | | | |

Phenotype terms and relation to functional alleles

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Term/Gene Category** | **Final Term\*** | **Functional Definition** | **Genetic Definition** | **Example diplotypes** |
| 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* (where N is ≥ 2) |
| 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*  *CYP2D6\*1/\*2* |
| Possible Intermediate Metabolizer | At least decreased enzyme activity (activity between normal and poor metabolizer) as this individual should be treated with “at least” the same precautions as would apply to an intermediate metabolizer | Combinations of one uncertain/unknown  function allele and decreased and/or no function alleles | *TPMT\*2/\*8*  *CYP3A5\*1/\*2* |
| 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*  *CYP2D6\*10/\*41*  *TPMT\*1/\*2* |
| Poor Metabolizer | Little to no enzyme activity | Combination of no function alleles and/or decreased function alleles | *CYP2C19\*2/\*2*  *CYP2D6\*4/\*5*  *TPMT\*2/\*3A* |
| 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* |
| Possible Decreased Function | At least decreased transporter activity (activity between normal and poor metabolizer) as this individual should be treated with “at least” the same precautions as would apply to and individual with decreased function. | Combinations of one uncertain/unknown  function allele and decreased and/or no function alleles | No examples to date |
| 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 |  |
| \*All terms should begin with the gene name (e.g., CYP2D6 Poor metabolizer, TPMT Normal metabolizer, SLCO1B1 Decreased Function) | | | | |

**Example of variant curation columns for a pharmacogenetic variant:**



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