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**Process for Assigning “Expert Panel” Designation on ClinVar**

**Approved by ClinGen Executive Committee, March 21, 2014**

The ClinVar database is hosted by NCBI and currently focuses on sharing variant-centric information. As part of this submission process the entity submitting the information is asked to provide an assertion with regard to “Clinical Significance”.

In order for users of ClinVar to have additional information with regard to the level of review of the submissions, ClinVar has developed a four star rating system (visible in the “Review Status” column). Currently, submitters default to the category of "single source" given the inability to stratify expertise on most submissions. However, submitters may apply for the status of "expert panel" according to the descriptions below.

**Expert Panel – Three Stars - Process**

The three star level description of the submitter refers to “Expert Panel” assertions. Groups seeking Expert Panel designation should submit the information described below using the attached form with regard to their variant evidence review process to clinvar@ncbi.nlm.nih.gov for review by the Clinical Genome Resource (ClinGen) program. This information will be reviewed by the appropriate ClinGen Clinical Domain Working Group (e.g., Cardiovascular or Germline Cancer) or ClinGen subcommittee and shared with the ClinGen Executive Committee to make thee determination of Expert Panel status for clinical assertions in ClinVar. The information provided on the Expert Panel request form will be posted on the ClinVar website to provide users of the site information about the groups obtaining the Expert Panel designation.

Information should be provided by filling out the ClinVar Expert Panel request form (maximum of 3 pages). Please make note of the following points:

1. It is recommended that the expert panel include individuals who are medical professionals caring for patients relevant to the disease gene in question, medical geneticists, clinical laboratory diagnosticians and/or molecular pathologists who report such findings and appropriate researchers relevant to the disease, gene, functional assays and statistical analyses.
2. It is expected that the individuals comprising the expert panel process should represent more than one academic or commercial institution.
3. Information should be provided with regard to any potential conflicts of interest of the panel members and how conflicts have been managed.
4. In addition to the one page summary requested here there should be more detailed information regarding the rules for variant classification available to the ClinGen investigators and the individuals accessing the assertions in ClinVar either through publication(s) in the medical literature and/or posting on a public website.
5. The completed form of any group assigned Expert Panel status will be made available on the ClinVar database website.

**Request for “Expert Panel” Designation on ClinVar**

**1. Name of Expert Panel (please write out any acronyms):**
Clinical Pharmacogenetics Implementation Consortium (CPIC)

**2. Date form submitted to** **clinvar@ncbi.nlm.nih.gov** **:\_\_**August 2, 2014\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**3. Contact name, institution and email address for one Expert Panel representative who will be the contact person for the ClinGen Executive Committee:

Teri E. Klein, PhD Kelly Caudle, PharmD, PhD**

**Stanford University St. Jude Children’s Research Hospital**

**teri.klein@stanford.edu****cpic@pharmgkb.org**

**3. Please provide member names, type of expertise, e.g. clinical, clinical laboratory, bioinformatic or research and institutional affiliation of the Expert Panel members using the table provided. Please note any individuals currently serving in a leadership role e.g. steering committee chairs.**

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| --- | --- | --- | --- |
| **Name** | **Institution** | **Expertise** | **Leadership Role** |
| Kelly E. Caudle, Pharm.D., Ph.D. | St. Jude Children’s Research Hospital | ClinicalResearch | CPIC Director |
| Mary V. Relling, Pharm.D. | St. Jude Children’s Research Hospital | ClinicalResearch | CPIC LeaderCPIC Steering Committee member |
| Teri E. Klein, Ph.D | Stanford University | ResearchBioinformatics | CPIC Co-LeaderCPIC Steering Committee memberDirector of PharmGKB |
| Julie A. Johnson, Pharm.D.  | University of Florida | ClinicalResearch | CPIC Steering Committee member |
| Dan M. Roden, M.D.  | Vanderbilt University | ClinicalResearch | CPIC Steering Committee member |
| Rachel F. Tyndale, Ph.D.  | University of Toronto and CAMH | Research | CPIC Steering Committee member |
| Michelle Whirl Carrillo, Ph.D. | Stanford University | ResearchBioinformatics | CPIC Informatics Co-Chair Associate Director, PharmGKB |
| James M. Hoffman, Pharm.D., MS | St. Jude Children’s Research Hospital | ClinicalResearchBioinformatics | CPIC Informatics Co-Chair  |
| Ellen M. McDonagh, Ph.D. | Stanford University | Research | Scientific Curator |
| Li Gong, Ph.D. | Stanford University | Research | Senior Scientific Curator |
| Katrin Sangkuhl, Ph.D. | Stanford University | Research | Senior Scientific Curator |
| Julia Barbarino, MSc | Stanford University | Research | Scientific Curator |
| Cyrine E. Haidar, Pharm.D. | St. Jude Children’s Research Hospital | Clinical |  |
| Kristine R. Crews, Pharm.D. | St. Jude Children’s Research Hospital | ClinicalResearch |  |

Listed above are CPIC leadership, CPIC members, and PharmGKB curators that review or are involved in the writing of most CPIC guidelines. However, all CPIC guidelines have writing committees with gene/drug specific expertise and include clinicians, scientists, pharmacologists, and informatics experts. Furthermore, the guideline draft is discussed on a CPIC conference call with all CPIC members (see https://cpicpgx.org/members/ for list of members) and circulated to the members for further review and approval. At each stage, feedback is considered for incorporation into the guideline and/or revision of the guideline, as supported by the available evidence and expert clinical judgment of the senior author and writing committee. Additionally, the guideline manuscript undergoes typical external scientific peer-review by the journal prior to publication.

**Management of Conflicts of Interest:** All authors declare all interests and activities potentially resulting in conflict of interest (COI) by written disclosure to the CPIC Steering Committee and writing committee before the approval of the authorship plan. Conflicts include NIH funding, that could be interpreted to indicate that authors are “advocates” of the enclosed recommendations, as well as any sources of revenue from patents, stock ownership, etc. All COIs are reported in the guideline manuscript. Each author with an established or possible COI should explain how their relationship(s) could influence the guideline development process or specific recommendations. The CPIC Steering Committee will be guided by the principles that (a) COIs must be transparent to all authors and readers (b) the majority of the authorship team should not have financial COIs (c) it is expected that CPIC guidelines will often have authors who are advocates for using test information to inform prescribing (d) COIs due to employment by an entity in clear conflict will be considered problematic (e) COIs involving senior and first authors are more problematic than those involving middle authors. Before submission for publication, each guideline will be reviewed by a CPIC member without any conflicts to evaluate the language, tone, and conclusions of the recommendation in light of the author(s)’ conflicts.

**4. One page summary of the process used by the Expert Panel with regard to making clinical assertions for genetic variants. Please note all genes currently under review by this process and any plans for future genes to be evaluated and assertions submitted to ClinVar.**Assignment of function to genetic variants and the therapeutic recommendation are based on the literature search conducted by the guideline writing committee. The PharmGKB Scientific Curator, the CPIC coordinator or authors with experience in literature or systematic review conduct the literature review and present the results to the writing committee. A search of PubMed and OVID MEDLINE is performed using the keywords for the gene and drug of interest, for example: (gene name) OR (gene symbol) OR (dbSNP rs number) OR (gene common names) AND (drug name OR drug class name). Furthermore, papers listed on PharmGKB are cross-checked as there may be annotations for the papers and/or additional publications. Examples of types of evidence reviewed include, but are not limited to, randomized clinical trials with pharmacogenetic-based prescribing versus dosing not based on genetics, pre-clinical and clinical studies demonstrating that drug effects or concentration are linked to functional pharmacogenetic loci, case studies associating rare variants with drug effects, in vivo pharmacokinetic/pharmacodynamics studies for drug or reference drug plus variant type, and in vitro metabolic and/or transport capacity for the drug plus variant type. Where available, evidence evaluating the outcomes when prescribing has been altered based on genetic testing is included.

Publications supporting a major finding are usually considered as a group and scored by members of the writing committee based on the totality of the evidence supporting that major finding. The rating scheme uses a scale modified slightly from Valdes et al.: high, evidence includes consistent results from well-designed, well-conducted studies; moderate, evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence; weak, evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

The writing committee discusses the evaluation of the literature and using the available evidence, decides how to define a phenotype (e.g. poor metabolizer) by first assigning variant alleles a functional group (normal function, decreased function, etc.). Each guideline contains a table that assigns likely function to relevant alleles and phenotypes based on possible genotypes. Only genetic variants in which there is at least a “moderate” level of evidence to support the functional status of that variant are included.

The writing committee also develops a draft therapeutic recommendation based on phenotype. CPIC’s therapeutic recommendations are based on weighing the evidence summarized in the supplementary Evidence Table from a combination of preclinical functional and clinical data, as well as on any existing consensus guidelines. To assign strength to a recommendation, CPIC uses a transparent three category system for rating recommendations that was adopted with slight modification from the rating scale for evidence-based recommendations on the use of antiretroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf). Therapeutic recommendations are graded as : strong, where “the evidence is high quality and the desirable effects clearly outweigh the undesirable effects”; moderate, in which “there is a close or uncertain balance” as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, in which the desirable effects of pharmacogenetic-based dosing are closely balanced with undesirable effects or the evidence is weak or based on extrapolations and there is room for differences in opinion as to the need for the recommended course of action; no recommendation, no recommendation, where there is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

For a list of current and planned CPIC genes/drugs see: https://cpicpgx.org/genes-drugs/. **5. Please list relevant publication(s) including PMID/PMCID which describe the variant classification process in detail and/or a publically accessible website which provides this information for the ClinGen Executive Committee and individuals using ClinVar:**

CPIC description: PMID 21270786

CPIC guideline develop process paper: PMID 24479687

CPIC guidelines: https://cpicpgx.org/guidelines/