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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 the 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):**

Pharmacogenomics Knowledge Base (PharmGKB)

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

**Stanford University**

**teri.klein@stanford.edu**

**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** |
| Teri E. Klein, Ph.D | Stanford University | ResearchBioinformatics | Director and PI of PharmGKBCo-Leader, CPIC |
| Russ B Altman, MD/Ph.D | Stanford University | ResearchMedical informatics | PI of PharmGKB |
| Michelle Whirl Carrillo, Ph.D. | Stanford University | ResearchBioinformatics | Associate Director, PharmGKBCo-Chair CPIC Informatics |
| Nancy Cox, PhD | University of Chicago | ResearchGenetics | Scientific Advisor for PharmGKB |
| David Haussler, PhD | University of California, Santa Cruz | ResearchBioinformatics | Scientific Advisor for PharmGKB |
| Julie A. Johnson, PharmD, FCCP, BCPS | University of Florida | Clinical Research | Scientific Advisor for PharmGKB |
| Michael Phillips | Precision Medicine Advisors | ResearchGenomics | Scientific Advisor for PharmGKB |
| Scott A. Waldman, MD, PhD, FCP | Thomas Jefferson University | Clinical Research | Scientific Advisor for PharmGKB |
| Mary V. Relling, Pharm.D. | St. Jude Children’s Research Hospital | ClinicalResearch | CPIC LeaderCPIC Steering Committee member |
| 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 |
| Maria Alvarellos, M.S. | Stanford University | Research | Scientific Curator |
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Listed above are PharmGKB leadership, PharmGKB scientific advisors and PharmGKB curators that read the literature and use manual curation to extract gene-drug-disease relationships from the pharmacogenetic literature. **Most importantly, our summarized pharmacogenomics knowledge (eg. drug-centered pathways, VIP gene summaries, drug dosing guidelines) are the results of collaboration with many experts in the fields.** They are also published in leading pharmacogenomics journals and undergo typical external scientific peer-review process 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) before publication of the manuscript. 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 PharmGKB and CPIC guideline manuscripts. Each author with an established or possible COI should explain how their relationship(s) could influence the PharmGKB annotation manuscripts, guideline development process or specific recommendations. Before submission for publication, each pharmgkb related manuscript will be reviewed by a member of the PharmGKB leadership team without any conflicts to evaluate the language, tone, and conclusions of the recommendation in light of the author(s)’ conflicts.

The contents of PharmGKB (https://www.pharmgkb.org) are curated through a set of procedures and standards that are freely available in writing at any time. Importantly, mechanisms for peer-review among PharmGKB curators are in place to ensure quality. PharmGKB has been funded by NIH for 15 years and has undergone a competitive peer review every 5 years. It is a term and condition of the grant award that the contents of PharmGKB are freely available for research purposes to all parties at any time. As a grant, the conflicts of interest are managed by the Stanford University Conflict of Interest policies (https://doresearch.stanford.edu/research-scholarship/conflicts-interest) and oversight, and the university keeps the NIH informed through consultation and by filing COI statements each year. At Stanford, the Office of Technology Transfer (contact – Imelda Oropeza, Copyright Licensing & Marketing Specialist, Office of Technology Licensing, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306, 650-725-9039 (direct), 650-725-7295 (fax), imelda.oropeza@stanford.edu) evaluates all opportunities to interact with and to license the contents of PharmGKB. A list of all licensees and their purposes is openly available at https://www.pharmgkb.org/downloads/ under License Reports.

We routinely disclose that PharmGKB has been licensed exclusively to Personalis Inc (http://www.personalis.com/) for commercial use to coincide with the grant period (ends June 2015), and Personalis also has the right to sublicense for commercial uses. Personalis is in the general business of genome sequencing for clinical uses. Dr. Altman is a founder and consultant to Personalis and Dr. Klein is a consultant to Personalis. They always disclose these relationships in all published papers and talks related to PharmGKB. However, Personalis does not have any influence on the contents of PharmGKB. Drs. Altman and Klein regularly report their activities to Stanford University.

**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.**

The Pharmacogenomics Knowledgebase (PharmGKB, [*http:www.pharmgkb.org*](http://www.pharmgkb.org))is a publically available knowledgebase that collects, curates, and disseminates information about the impact of human genetic variation on drug responses. It provides comprehensive catalog of genes and genetic variations that are most important for drug response (many directly linked to drug efficacy and toxicity). PharmGKB presents knowledge in the forms of variant and clinical annotations, drug dosing guidelines, pathway diagrams and Very Important Pharmacogene (VIP) gene summaries. These annotations are manually curated by PhD/MS level scientific curators from primary pharmacogenomic literature and are products of collaboration with external scientific experts. We have developed standard operating procedures for our curation process to ensure data accuracy, completeness and consistency. Our pathways, VIPs and dosing guidelines are written in collaboration with experts in the fields and many are published in peer reviewed leading pharmacogenomics journals.

Variant annotations are the core component of the knowledgebase and each variant annotation is based on a published article and describes the reported association between a single variant (single-nucleotide polymorphism or haplotype) and a drug phenotype. Each variant annotation includes key study parameters such as study size, ethnicity, allele frequency and statistics (e.g., P value and odds ratio). They are also constructed using uniform sentences and standardized terminology to allow for seamless integration with other components of our database as well as allow for seamless integration with other research/clinical databases.

Building on variant annotations, PharmGKB “clinical annotations” combine multiple-variant annotations into a single summary of genotype-based variant–drug–phenotype association. Each Clinical annotation is assigned a level of evidence depending on specific criteria, including study size, replication, implementation status and statistical relevance of the association (P-value and odds ratio, etc.). Clinical annotations may also move up or down the evidence scale if new variant annotations provide further evidence for the association, if the association becomes implemented in the clinic, or contradictory findings are published. We currently have four levels of evidence for clinical annotations. Level 1 annotations involve a variant–drug combination in which the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant P values and, preferably, with a strong effect size. Level 2 annotations are for variant–drug combinations with moderate evidence of an association, must be replicated but may include negative studies. Level 3 annotations are based on a single significant (not yet replicated) study or association evaluated in multiple studies but lacking clear evidence of an association. Level 4 annotations are based on a case report; on a study that did not achieve significance but is biologically plausible; or on *in vitro*, molecular, or functional assay evidence. The evidence scale provides a clear measure of confidence in the drug-variant association and is easily interpretable by clinicians and researchers. These criteria have gone through multiple rounds of improvements based on feedbacks from our scientific advisors as well as other experts from the field. Variant annotations are added as new papers come out and clinical annotations are reviewed and revised as new evidence come out.

PharmGKB works closely with the Clinical Pharmacogenetics Implementation Consortium (CPIC) from the start of the shared project. PharmGKB assigns at least one Scientific Curator to each CPIC guideline writing committee to search, compile and evaluate the evidence for the gene-drug pair. Curators take primary responsibility for completing background gene and drug summaries, conducting literature review, assigning likely phenotypes based on genotypes, as well as preparing supplementary materials for each guideline. CPIC guidelines are simultaneously published and maintained on PharmGKB website, in both plain text as well as computable form for easy integration into clinical decision support tools.

For a list of current PharmGKB clinical annotations: <http://www.pharmgkb.org/search/clinicalAnnotationList.action?levelOfEvidence=top>

For a list of well known Pharmacogenomic Associations:

<http://www.pharmgkb.org/search/knownPairs.action>

For a list of PGx drug dosing guidelines:

<http://www.pharmgkb.org/view/dosing-guidelines.do>

For a list of PharmGKB VIP genes:

<http://www.pharmgkb.org/search/browseVip.action?browseKey=vipGenes>

For a list of PharmGKB pathways:

<http://www.pharmgkb.org/search/browse/pathways.action>

**Sample ClinVar Submission was provided. 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:**

 **PharmGKB annotation process description**: PMID 22992668

 **PharmGKB description:** PMID 23824865

**PharmGKB pathways:** PMID 24915143, 24849324, 24625462, 24220207, 24128936, 23962908, 23913015, 23788015, 23407051, 22960662, 2722338, 22569204, 22336956, 22293536, 21738081, 21546862, 21317831, 20938371, 20440227, 20124951, 20023594, 19952870, 19741567, 19525887, 19512958, 19512957, 19512956, 21048526, 24401834

**PharmGKB VIPs:** PMID 24892773, 24681965, 24492252, 23962911, 23962910, 22643671, 22588316, 22547082, 22407409, 22237549, 22027650, 21989077, 21063235, 20648701, 20216335, 20154640, 20084049, 19927042, 19898265, 19451861, 19512959, 20739908, 20736885, 20150828, 20811316, 19952871, 19940803

**CPIC guidelines:** PMID 22378157, 24561393, 23232549, 23486447, 21270794, 23422873, 23695185, 21716271, 23698643, 22205192, 24458010, 24598717, 24787449, 22617227, 24918167, 21900891, 23988873, 24096968