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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):** The Clinical and Functional TRanslation of CFTR (CFTR2) Team

**2. Date form submitted to** **clinvar@ncbi.nlm.nih.gov** **:** 17 June 2015**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

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

kraraigh@jhmi.edu

**4. 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** |
| **CFTR2 Team** |
| **Garry Cutting, MD** | Johns Hopkins University, Baltimore, MD, USA | Clinical laboratoryResearch | Project director |
| **Carlo Castellani, MD** | Ospedale Civile Maggiore, Verona, Italy | Clinical |  |
| **Mary Corey, PhD** | The Hospital for Sick Children, Toronto, ON, Canada | Research  |  |
| **Johanna Rommens, PhD** | The Hospital for Sick Children, Toronto, ON, Canada | Research |  |
| **Patrick Sosnay, MD** | Johns Hopkins University, Baltimore, MD, USA | Clinical |  |
| **Michelle Lewis, MD, JD** | Johns Hopkins University, Baltimore, MD, USA | Research |  |
| **Chris Penland, PhD** | US Cystic Fibrosis Foundation, Bethesda, MD, USA | Research |  |
| **Karen Raraigh, MGC** | Johns Hopkins University, Baltimore, MD, USA | Research |  |
| **CFTR2 Clinical Expert Panel** |
| **Christiane De Boeck, MD, PhD** | University Hospital of Leuven, Leuven, Belgium | Clinical |  |
| **Peter Durie, MD** | The Hospital for Sick Children, Toronto, ON, Canada | ClinicalResearch |  |
| **Stuart Elborn, MD** | Queen’s University, Belfast, UK | Clinical |  |
| **Philip Farrell, MD, PhD** | University of Wisconsin, Madison, WI, USA | Clinical |  |
| **Michael Knowles, MD** | University of North Carolina, Chapel Hill, NC, USA | ClinicalResearch |  |
| **Isabelle Sermet, MD, PhD** | Necker Hospital, Paris, France | ClinicalResearch |  |
| **CFTR2 Functional Studies Expert Panel** |
| **Margarida Amaral, PhD** | Universidad de Lisboa, Lisboa, Portugal | Research |  |
| **David Sheppard, PhD** | University of Bristol, Bristol, UK | Research |  |
| **Phillip Thomas, PhD** | University of Texas Southwestern, Dallas, TX, USA | Research |  |
| **Frederick van Goor, PhD** | Vertex Pharmaceuticals Inc., San Diego, CA, USA | Research |  |
| **Robert Bridges, PhD** | Chicago Medical School, Chicago, IL | Research |  |
| **Gergely Lukacs, PhD** | McGill University, Monreal, Quebec, Canada | Research |  |

**5. 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.**Genes under review: *CFTR*

Process used:

Data from patients followed in a CF clinic is collected from registries and clinics without a national registry from all over the world. The most recent data collection contains 88,664 patients from 41 countries. De-identified data collected includes basic demographics, *CFTR* mutations, and clinical characteristics (sweat chloride, lung function, use of pancreatic enzymes, etc.). Mutations reported in this group of patients are then prioritized by frequency and analyzed using three main criteria: clinical parameters of patients carrying a mutation, functional analysis to assess the consequence of a given nucleotide change, and population/penetrance studies.

* *Clinical criteria to declare a mutation CF-causing:* Data from various registries is combined into our central, de-identified CFTR2 dataset. Clinical data, with an emphasis on sweat chloride measurements, from patients with a given mutation of interest *in trans* with a known CF-causing mutation are examined. Sweat chloride is emphasized because it is standardized, less-affected by age than other phenotypes, and directly correlates with the degree of CFTR impairment, therefore allowing more straightforward delineation of disease.
* *Functional criteria to evaluate mutation severity:* We have coordinated a systematic assessment of CFTR function in cell models. Mutations predicted to introduce a premature termination codon are presumed to cause significant dysfunction and are not evaluated experimentally. Mutations resulting in an amino acid substitution or an in-frame insertion/deletion are evaluated in multiple cell lines. Cell lines having low levels of mature (C band) CFTR (<10% of WT-CFTR levels), and/or low CFTR current (<10% of WT-CFTR levels) met functional criteria as CF-causing.
* *Population studies to evaluate mutations:* As a third line of evidence to evaluate the disease liability of mutations, comparisons were made between the allele frequencies in our CFTR2 population, healthy population controls from 1000 Genomes, and obligate heterozygotes (fathers of CF offspring). Variants observed in fathers of CF offspring *in trans* with a known CF-causing mutation (transmitted to the affected child) were deemed non CF-causing.

Variants having undergone evaluation are deemed CF-causing, non CF-causing, or as having varying clinical consequences. This characterization and aggregate clinical data from patients carrying specific *CFTR* mutations are published online at <http://cftr2.org>.

**6. 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:**

<http://cftr2.org>

Sosnay P, et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. *Nat Genet* 2013:45(10);1160-7. PMID 23974870.

Sharma N, et al. Experimental assessment of splicing variants using expression minigenes and comparison with in silico predictions. *Hum Mutat* 2014:35(10);1249-59. PMID 25066652.