Genetic Database Recognition Decision Summary for

ClinGen Expert Curated Human Variant Data

Genetic Database Name: ClinGen Expert Curated Human Variant Data

Submission Number: Q181150

Summary of FDA Review to Support Recognition

The ClinGen Expert Curated Human Variant Data qualifies as a database per FDA's guidance document, "*Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-based In Vitro Diagnostics*".

To support recognition of the Clinical Genome Resource (ClinGen) Expert Curated Human Variant Data, ClinGen submitted variant assertions and the evidence that supports them as well as the oversight and governance procedures for creating, maintaining, and expanding the currently available variant assertions within the scope described below. These assertions and procedures are publicly available. FDA evaluated whether these procedures provide reasonable assurance that the variant assertions made using the procedures are accurate and could be used as a source of valid scientific evidence in support of clinical validity of genetic and genomic-based tests in regulatory submissions. This evaluation was based upon whether ClinGen demonstrated conformance with the recommendations described in FDA's guidance document, "*Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-based In Vitro Diagnostics*". Based upon the information reviewed, the FDA determined that the ClinGen Expert Curated Human Variant Data conforms to the recommendations described in the guidance. FDA's review of the information provided is described herein.

The FDA concludes that the ClinGen Expert Curated Human Variant Data procedures provide reasonable assurance that assertions from the database constitute valid scientific evidence that can be used to support clinical validity of genetic tests in future premarket submissions and therefore, FDA recognizes the ClinGen Expert Curated Human Variant Data for the scope described below.

Scope of Recognition

This recognition is for the ClinGen Expert Curated Human Variant Data variant classifications and the processes that support them for germline variants for hereditary disease where there is a high likelihood that the disease or condition will materialize given a deleterious variant (i.e., high penetrance).

Summary of Genetic Database Operations and Procedures to Support Recognition

ClinGen is a National Institutes of Health (NIH)-funded resource intended to aggregate, curate, and making publicly available information pertaining to the clinical significance of genotype-phenotype associations.

The ClinGen Expert Curated Human Variant Data is publicly available at www.clinicalgenome.org. Variant assertions are publicly available within the ClinGen evidence repository, also on www.clinicalgenome.org, and via ClinVar, a freely accessible, web-based public archive of reports of the relationships among genetic variants and phenotypes. ClinVar is funded and maintained by NIH's National Center for Biotechnology Information, part of the National Library of Medicine.

ClinGen Expert Curated Human Variant Data is the collection of variant assertions, and the evidence supporting those assertions, that have been fully evaluated and determined by ClinGen governed Variant Curation Expert Panels (VCEPs). ClinGen creates and maintains oversight and governance

procedures for VCEPs which are composed of individuals with scientific expertise regarding gene function, clinical expertise regarding disease manifestations, and biocurators who are trained in evaluating evidence sources that support a variant assertion. VCEPs carry out robust variant curation and assessment for a single gene or set of genes associated with a single disease/condition or set of related diseases/conditions in accordance with the procedures described by ClinGen.

ClinGen Oversight and Governance

The following entities facilitate ClinGen's oversight and governance of VCEPs:

- The ClinGen Steering Committee is responsible for establishing standards and oversight of all processes within the scope of ClinGen. Steering Committee membership is composed of the principal investigators at each of the funded ClinGen institutions, leadership from various ClinGen working groups and committees, and a program officer.

- The ClinGen Clinical Domain Working Groups Oversight Committee (CDWG Oversight Committee) has responsibility for the general oversight of the development, approval and coordination of VCEPs. Membership in the CDWG Oversight Committee includes representatives from the Steering Committee, VCEP leaders, and coordinators.

- The Sequence Variant Interpretation (SVI) workgroup consists of experts in the methods of human variant interpretation, and, in particular, the application of the ACMG/AMP human variant interpretation guidance which represents the joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, which is described in *Richards et al. 2015. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genetics in Medicine. 17, 405-423* (further referenced as Richards et al. herein). The SVI is responsible for providing guidance to ClinGen for all variant assessment activities. This includes education for the VCEPs regarding the ACMG/AMP criteria and highlighting where gene/disease-specific clarifications may be appropriate.

ClinGen creates and maintains oversight and governance procedures for VCEPs which includes a standard operating procedure (SOP), the *ClinGen Variant Curation Expert Panel Protocol*, that describes the following:

- requirements for membership and training,
- policies for addressing conflicts of interest,
- processes for determining modifications to American College of Medical Genetics criteria/rules (originally published in Richards et al.),
- processes for validation of modified ACMG criteria,
- processes for variant curation and final assertion of pathogenicity,
- submission of variant classification to ClinVar,
- re-evaluation of variant assertions,
- and processes regarding conflicting assertions.

This SOP that the VCEPs follow is made publicly available on ClinGen's website, www.clinicalgenome.org. The information provided in this SOP is further described in Sections A through K below.

The following ClinGen resources are utilized by the VCEPs to ensure consistency and quality of variant curation and assertions between VCEPs:

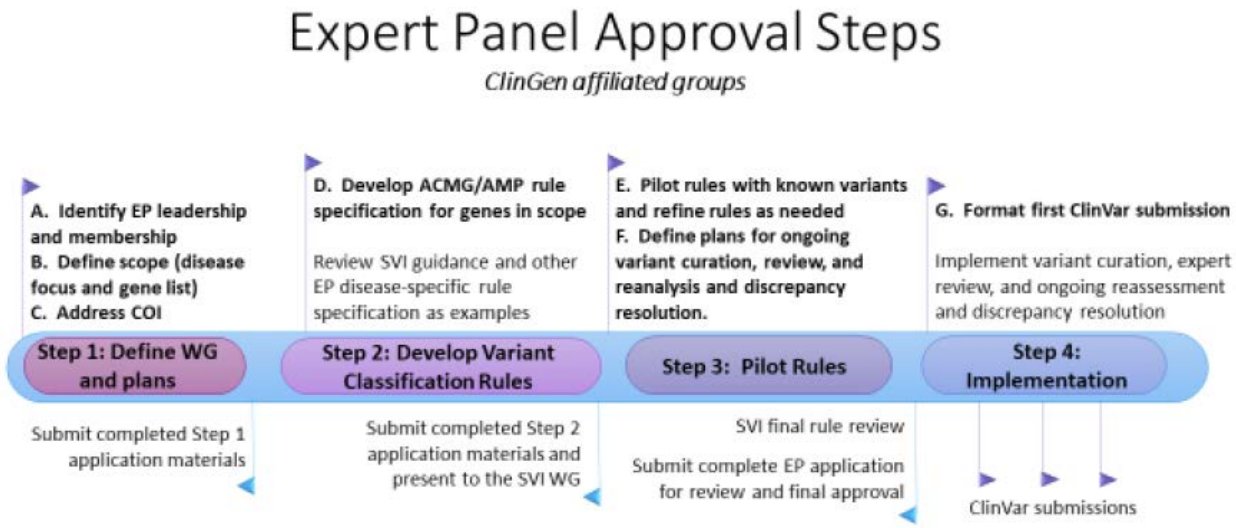
- The ClinGen Allele Registry provides unique identifiers ("CAids" or "canonical identifiers")

for genetic variants. These identifiers and additional web services provided by the Registry ensure unique naming and consistent identification of genetic variants. The Registry provides web services that help retrieve an existing identifier or assign a new identifier based on unique combinations of variant attributes. The Registry also links to alternate identifiers already established in major public databases.

- The Variant Curation Interface (VCI) aggregates external evidence about variants and supports the manual curation of variant information. Supporting evidence is accessible to all VCI users. The data fields within the VCI are defined by the evidence categories provided by Richards et al. Dynamic links to external information sources are also embedded within the relevant evidence tabs. External information sources are defined for each evidence category as outlined in Richards et al. as well as additional resources identified as valid sources by the SVI.

VCEP Approval Process

The development, coordination, and maintenance of VCEPs require step-wise approval in a controlled process under the purview of ClinGen oversight committees as depicted below.



Candidate VCEPs develop weighted pathogenetic and benign criteria/rules for variant evaluation that are gene/disease/condition-specific criteria that are modified from criteria/rules originally reported in Richards et al. Criteria/rules are weighted based on the strength of evidence needed to meet a specific criterion/rule. These criteria are then combined using a tiered system to assign a pathogenicity assertion (i.e., an interpretation of clinical significance of the variant). The criteria are combined according to the five ACMG/AMP recommended classifications/assertions, as described in Richards et al.: pathogenic (P), likely pathogenic (LP), uncertain significance (VUS), likely benign (LB), and benign (B). This is further described in Sections A. and B. below.

Although most VCEPs use the rules defined in Table 5 of Richards et al. for combining criteria to assign a final assertion, VCEPs can seek approval from the ClinGen oversight committee to modify the rules for combining criteria. In addition, VCEPs may make a case-by-case variant-level decision to override the calculated classification that would be made using the Table 5 rules for combining criteria. In these cases, the VCEPs decision is clearly documented in the evidence summaries provided on ClinVar and in ClinGen's evidence repository (see example summary in Section C below).

VCEPs validate the modified criteria using known variants of differing pathogenicity and differing types of evidence. Upon successful validation, the VCEP submits the modified criteria to the ClinGen

rule specification review committee for approval. If the modified criteria/rules are approved, the VCEP is considered an approved ClinGen VCEP. The modified criteria/rules for each VCEP are made publicly available on each VCEP webpage hosted on ClinGen's website, www.clinicalgenome.org, and used to curate evidence. The approved rules are used for variant evaluation and to determine final variant assertions.

Each VCEP is responsible for developing variant evidence summaries that promote understanding of the evidence used to support the assertion and enable external review. The evidence summaries are made in clear and understandable language and include the pathogenicity classification, the evidence supporting the application of each criterion, and the reason for applying each criterion. These statements include, where applicable, reference to the external data sources used in the curation and classification. These evidence summaries are provided in the summary evidence tab in ClinVar. They are also accessible within ClinGen's evidence repository, which is publicly accessible to all users.

Reanalysis and Reevaluation

VCEPs regularly reevaluate their variant assertions. VCEPs revaluate likely pathogenic and variants of unknown significance every two years. Likely benign classifications are reviewed when new population datasets are released. If VCEPs do not maintain their interpretations within the timeframes specified by ClinGen, the VCEP may lose their VCEP status. Assertions are versioned within the VCI, described below.

VCEPs expedite the reassessment of variants that have a conflicting assertion submitted to ClinVar after the VCEP's variant submission. For medically significant differences, i.e., a change from pathogenic/likely pathogenic to variant of unknown significance/likely benign/benign, the VCEP will contact the submitter that provided the information to ClinVar within 3 months to attempt to resolve the difference. If the submitter provides criteria and evidence in support of the discrepant classification, the VCEP and SVI will review the criteria for alignment with variant assertion guidelines outlined in Richards et al. and those specified by the VCEP. The VCEP will also provide the VCEP's classification and curated evidence to the external submitter. The VCEP will re-evaluate the variant using all appropriate new information from the inquiry. If the VCEP assertion is changed, it will be updated in ClinVar within one month of the final assertion being made.

Mechanism for Assertion Feedback

To facilitate feedback on assertions made by the VCEP, variant assertions made available in ClinVar and the Evidence Repository on www.clinicalgenome.org, are linked to the respective VCEP webpage hosted on ClinGen's website. Public feedback on the assertions can be made via a comment box on the VCEP website. Furthermore, the contact for each VCEP is available on ClinGen's website. Upon receipt of feedback on an assertion, the VCEP will re-evaluate the variant using all appropriate new information from the inquiry. If the VCEP assertion is changed, it will be updated in ClinVar within one month of the final assertion being made.

Criteria Evaluated That Support Recognition

FDA evaluated ClinGen's oversight and governance procedures and the procedures, variant assertions and evidence that supports them, for three representative VCEPs (Inherited Cardiomyopathy, RASopathy, and phenylalanine hydroxylase (PAH)), to determine if recognition was appropriate. That review is described herein.

A. Variant Evaluation

Information from publicly available sources and laboratory data is curated and scored with respect to the variant-disease relationship, according to disease or gene specifications (i.e., modified ACMG/AMP rules, see description above) developed by the respective VCEP and approved by the ClinGen SVI and the CDWG Oversight Committee. Please refer to Section H. Metadata for a description of evidence sources used for variant evaluation.

ClinGen requires that any approach used for variant curation and preliminary evaluation must include at least two reviewers. Biocurators enter data into the VCI and perform baseline curation. Biocurators evaluate the evidence to determine which of the modified ACMG/AMP criteria/rules developed by the VCEP are met and provide an evaluation statement for applying or not applying an evidence criteria/rule to the variant. These statements include reference to the supporting data that were evaluated for the specified rule. The criteria/rules evaluated by biocurators during variant evaluation are weighted as standalone, very strong, strong, moderate, or supporting. The weighted rules are then combined to determine a classification, further described below in Section B. Assertion. An example of the Inherited Cardiomyopathy VCEP modified ACMG/AMP pathogenic and benign rules for variant evaluation is shown in the tables below.

Pathogenic Criteria		
Rule		Rule Description
Strong	PS1	Different nucleotide change (same amino acid) as a previously established pathogenic variant
	PS2	*De novo* (paternity confirmed) in a patient with disease and no family history.
	PS3	Functional studies of mammalian knock-in models supportive of a damaging effect on the gene or gene product
	PS4	Prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls—OR—variant identified in ≥ 15 probands with consistent phenotypes
	PP1_Strong	Variant segregates with ≥ 7 meioses
Moderate	PM1	Hotspot/est. functional domain (amino acids 181-937) without benign variation
	PM2	Absent/extremely rare (<0.004%) from large population studies
	PM4	Protein length changes due to in-frame deletions/insertions of any size in a non-repeat region or stop-loss variants
	PM5	Missense change at an amino acid residue where a difference missense change previously established as pathogenic
	PM6	Confirmed *de novo* without confirmation of paternity
	PVS1_Moderate	Null variant in gene with evidence supporting LOF as disease mechanism
	PS4_Moderate	Variant identified in ≥ 6 probands with consistent phenotypes
	PP1_Moderate	Variant segregates in ≥ 5 meioses
Supporting	PP1	Variant segregates in ≥3 meisoes
	PP3	Multiple lines of computation evidence support a deleterious effect on the gene or gene product
	PS4_Supporting	Variant identified in ≥2 probands with consistent phenotypes

Benign Criteria		
Rule		Rule Description
SA*	BA1	Allele frequency ≥ 0.1% based on the filtering allele frequency (FAF) in ExAc
Strong	BS1	Allele frequency ≥0.02% based on the filtering allele frequency (FAF) in ExAc provided there is no conflicting information
	BS4	Functional studies of mammalian knock-in models supportive of no damaging effect on protein function or splicing
	BS4	Non-segregation in affected members of a family
Supporting	BP2	Observed as compound het (in trans) or double het in genes with overlapping function (e.g., sarcomere genes) without increased disease severity—OR—observed in cis with a pathogenic variant in any inheritance pattern
	BP4	Multiple lines of computational evidence suggest no impact on gene or gene product
	BP5	Variant found in a case with an alternate molecular basis for disease
	BP7	A silent variant for which splicing prediction algorithms predict no impact to the splice consensus sequence not the creating of a new splice site—AND—the nucleotide is not highly conserved

* SA = Standalone

The ClinGen requirements for VCEP variant evaluation are described in the ClinGen Variant Curation Expert Panel Protocol which is made publicly available on ClinGen's website, www.clinicalgenome.org. ClinGen also maintains a publicly available General Variant Curation Standard Operating Procedure (SOP) that describes best practices for curating variant-phenotype relationships.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes that the ClinGen oversight procedures and the protocols and variant evaluation for three representative VCEPs (Inherited Cardiomyopathy, RASopathy, and phenylalanine hydroxylase (PAH)), demonstrate that publicly available and validated protocols are used for variant evaluation.

B. Assertions

The VCI programmatically aggregates all the applied criteria/codes and calculates a tentative variant classification of pathogenicity (i.e., assertion) based on the combining criteria/rules described in Table 5 from Richards et al. The criteria are combined according to the five ACMG/AMP recommended classifications/assertions, as described in Richards et al.: pathogenic (P), likely pathogenic (LP), uncertain significance (VUS), likely benign (LB), and benign (B). The curator either selects the calculated classification, or makes a different recommendation, to present for final review.

The baseline curation is reviewed and preliminarily classified by either two blinded domain experts (if only one biocurator performed initial curation) or the full VCEP (if two curators perform independent assessments). In the scenario where two domain experts review the initial curation for an initial assertion, a full VCEP review is triggered if the experts do not reach consensus, either expert raises concerns regarding an applied rule, or the strength of the functional evidence needs further input from the VCEP.

Final decisions regarding variant assertions are made by consensus of the VCEP. Consensus is achieved if there is either unanimous agreement by all members or majority vote in favor. Variant classifications require at least a majority vote (individual VCEPs may have higher quorum requirements) to be published as an approved assertion. If a majority vote is not obtained, the variant will either be considered an unclassified variant or VCEPs may decide to err on the side of conservativeness in these situations and classify using the more conservative class (e.g. agree that a variant will be considered VUS if a majority vote is not obtained for a LP or LB classification). "Unclassified variants" are re-evaluated every 2 years to determine if additional evidence is available to support classification. Final approval by the VCEP is required for all variant assertions. The approval of the assertion is recorded in the VCI and the variant record is labeled as "Approved."

Assertions made by each VCEP are publicly available through ClinVar and ClinGen's Evidence Repository. Please refer to Section C below regarding the information that is made publicly available for each variant assertion.

The VCEP will undergo a review of their specified ACMG/AMP criteria on an annual basis or as appropriate based on new gene-specific knowledge or SVI work group criteria guidance. This process will include consideration of any new guidance put forth by the SVI as well as updates to scientific and clinical knowledge about the characteristics of the particular disease/gene(s) group. Any changes/revisions made to the VCEP's specified criteria must be approved by review of the SVI work group and the CDWG Oversight Committee.

During review of the changes, the VCEP is expected to present evidence supporting/justifying the rule change as well as how it does or does not impact all previously classified variants.

Any modifications to prior, published VCEP ACMG/AMP classification criteria will be made public via presentation at professional education conferences and/or via publication in peer-reviewed journals. These will also be updated on ClinVar and on the VCEP page of the ClinGen website. Variant assertions are also versioned in the VCI.

FDA evaluated the VCEP-specific modified criteria/codes, the combining criteria used to evaluate evidence and determine variant classifications, and the final variant assertions for three representative VCEPs: Inherited Cardiomyopathy, RASopathy, and phenylalanine hydroxylase (PAH). The protocols of, and variant assertions made by, these representative VCEPs were reviewed to evaluate whether the protocols adequately produce high-confidence assertions and if the type of data evaluated in the VCEP protocols is similar to the type of information that would typically be evaluated during FDA review of clinical validity for genetic tests intended to report variants within the scope of this recognition. FDA further evaluated whether the protocols and assertions made by the three representative VCEPs could be extrapolated to other VCEPs.

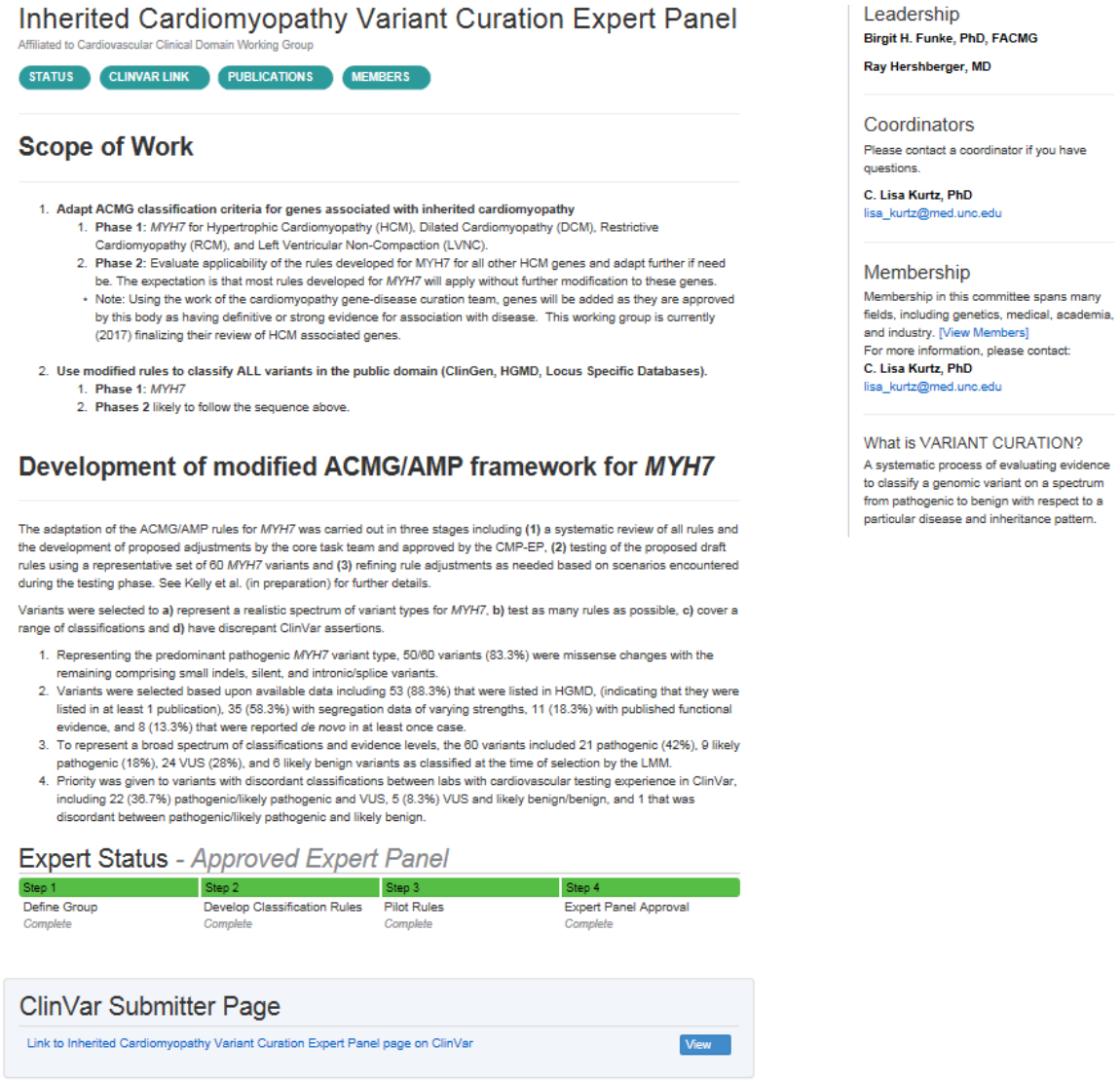
Based upon the information reviewed, the variant assertions and the evidence that supports them, for each of the three representative VCEPs demonstrate the ClinGen Expert Curated Human Variant Data procedures are robust across inheritance patterns (i.e., autosomal dominant and autosomal recessive), across variant types (i.e., gain-of-function, loss-of-function), and across the five pathogenicity classifications. Thus, the protocols and variant assertions by the three VCEPs provided for review are representative of the variant types for VCEPs that are within the scope of recognition for the ClinGen Expert Curated Human Variant Data. The evidence sources and tiered system of pathogenicity classification are highly consistent with the type of information that is reviewed by FDA in support of clinical validity for these types of variants.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes that ClinGen's governing procedures and the VCEP-specific procedures for variant evaluation and assertion demonstrate that multiple lines of evidence are evaluated, evidence is appropriately weighted, strong evidence is used to make assertions, and the protocols for variant evaluation and assertion have been validated for the ClinGen Expert Curated Human Variant Data.

C. *Transparency and Public Accessibility*

ClinGen's governing SOPs and VCEP-specific information for variant evaluation and assertion are made publicly available. All final variant assertions, and the summary evidence supporting the final assertion, are made publicly available through ClinVar and on ClinGen's website, www.clinicalgenome.org, through the Evidence Repository. The location of publicly accessible information that demonstrates transparency of the final assertions, and the ClinGen and VCEP procedures, are described herein.

Each VCEP has a page hosted on ClinGen's website that describes the members of the VCEP, the scope of the work, the development of modified ACMP/AMP framework for the VCEP and links to the modified ACMG/AMP criteria used by the VCEP and the ClinVar submitter page, for example, as depicted in the image below.



Inherited Cardiomyopathy Variant Curation Expert Panel

Affiliated to Cardiovascular Clinical Domain Working Group

STATUS | CLINVAR LINK | PUBLICATIONS | MEMBERS

Scope of Work

1. **Adapt ACMG classification criteria for genes associated with inherited cardiomyopathy**
   1. **Phase 1**: *MYH7* for Hypertrophic Cardiomyopathy (HCM), Dilated Cardiomyopathy (DCM), Restrictive Cardiomyopathy (RCM), and Left Ventricular Non-Compaction (LVNC).
   2. **Phase 2**: Evaluate applicability of the rules developed for MYH7 for all other HCM genes and adapt further if need be. The expectation is that most rules developed for *MYH7* will apply without further modification to these genes.
   - Note: Using the work of the cardiomyopathy gene-disease curation team, genes will be added as they are approved by this body as having definitive or strong evidence for association with disease. This working group is currently (2017) finalizing their review of HCM associated genes.

2. **Use modified rules to classify ALL variants in the public domain (ClinGen, HGMD, Locus Specific Databases).**
   1. **Phase 1**: *MYH7*
   2. **Phases 2** likely to follow the sequence above.

Development of modified ACMG/AMP framework for *MYH7*

The adaptation of the ACMG/AMP rules for *MYH7* was carried out in three stages including **(1)** a systematic review of all rules and the development of proposed adjustments by the core task team and approved by the CMP-EP, **(2)** testing of the proposed draft rules using a representative set of 60 *MYH7* variants and **(3)** refining rule adjustments as needed based on scenarios encountered during the testing phase. See Kelly et al. (in preparation) for further details.

Variants were selected to **a)** represent a realistic spectrum of variant types for *MYH7*, **b)** test as many rules as possible, **c)** cover a range of classifications and **d)** have discrepant ClinVar assertions.

1. Representing the predominant pathogenic *MYH7* variant type, 50/60 variants (83.3%) were missense changes with the remaining comprising small indels, silent, and intronic/splice variants.
2. Variants were selected based upon available data including 53 (88.3%) that were listed in HGMD, (indicating that they were listed in at least 1 publication), 35 (58.3%) with segregation data of varying strengths, 11 (18.3%) with published functional evidence, and 8 (13.3%) that were reported *de novo* in at least once case.
3. To represent a broad spectrum of classifications and evidence levels, the 60 variants included 21 pathogenic (42%), 9 likely pathogenic (18%), 24 VUS (28%), and 6 likely benign variants as classified at the time of selection by the LMM.
4. Priority was given to variants with discordant classifications between labs with cardiovascular testing experience in ClinVar, including 22 (36.7%) pathogenic/likely pathogenic and VUS, 5 (8.3%) VUS and likely benign/benign, and 1 that was discordant between pathogenic/likely pathogenic and likely benign.

Expert Status - *Approved Expert Panel*

Step 1	Step 2	Step 3	Step 4
Define Group	Develop Classification Rules	Pilot Rules	Expert Panel Approval
Complete	*Complete*	*Complete*	*Complete*

ClinVar Submitter Page

Link to Inherited Cardiomyopathy Variant Curation Expert Panel page on ClinVar — View

Leadership

Birgit H. Funke, PhD, FACMG

Ray Hershberger, MD

Coordinators

Please contact a coordinator if you have questions.

C. Lisa Kurtz, PhD
lisa_kurtz@med.unc.edu

Membership

Membership in this committee spans many fields, including genetics, medical, academia, and industry. [View Members]
For more information, please contact:
C. Lisa Kurtz, PhD
lisa_kurtz@med.unc.edu

What is VARIANT CURATION?

A systematic process of evaluating evidence to classify a genomic variant on a spectrum from pathogenic to benign with respect to a particular disease and inheritance pattern.

Each VCEP also has a submitter page on ClinVar (hyperlinked from the VCEP page hosted on www.clinicalgenome.org) that provides summary information on the VCEP and contact information (name, phone number and email) for the VCEP. The submitter page includes links to documentation for the disease/condition-specific ACMG/AMP criteria developed by the VCEP, the variants that have been classified by the VCEP, and the VCEP page hosted on the ClinGen website, for example, as depicted in the image below.

ClinGen Inherited Cardiomyopathy Expert Panel, CMP-EP

General information

ClinGen Inherited Cardiomyopathy Expert Panel, CMP-EP

Cambridge
Massachusetts
United States
https://www.clinicalgenome.org/working-groups/clinical-domain/cardiovascular-clinical-domain-working-group/myh7-variant-curation-expert-panel/
Organization ID: 506161

Expert panel documentation

ftp://ftp.ncbi.nlm.nih.gov/pub/clinvar/ClinGen/expert_panels/ClinGen_Inherited_Cardiomyopathy/

Personnel

Birgit Funke, Lab Director
Phone: 6177688467
Email: bfunke@bwh.harvard.edu

Assertion criteria

Level: Expert panel

ACMG variant classification (MYH7)

Summary of submissions to ClinVar

Total submissions: 102

Gene

Gene	Submissions	Last Updated
MYH7	102	Jul 28, 2017

Condition

Name	Submissions	Last Updated
Ebstein's anomaly of the tricuspid valve	1	Jul 28, 2017
Familial restrictive cardiomyopathy	2	Jul 28, 2017
Primary dilated cardiomyopathy	6	Jul 28, 2017
Primary familial hypertrophic cardiomyopathy	30	Jul 28, 2017
not specified	64	Jul 28, 2017

Variant-level Pathogenicity Assertions. All final assertions regarding the pathogenicity of a genomic variant are publicly available on ClinVar.

The final assertions available to view on ClinVar include the following information:

- Pathogenicity assertion using standard language: Benign, Likely Benign, Uncertain Significance, Likely Pathogenic, Pathogenic
- Disease or condition name and inheritance pattern for which the pathogenicity assertion applies
- Summary of the asserted pathogenicity classification and the evidence categories applied
- Date of evaluation
- Name of ClinGen Variant Curation Expert Panel that made the assertion

An example of a ClinVar variant record for an assertion made by a VCEP is depicted below.

Assertion and evidence details Go to:

Clinical assertions | Summary evidence | Supporting observations

Germline

Filter:

Clinical significance (Last evaluated)	Review status (Assertion method)	Collection method	Condition(s) (Mode of inheritance)	Origin	Citations	Submitter - Study name	Submission accession
Pathogenic (Dec 15, 2016)	reviewed by expert panel · ACMG variant classification (MYH7)	curation	Primary familial hypertrophic cardiomyopathy (Autosomal dominant inheritance) [MedGen | Orphanet | Orphanet | OMIM]	germline	· PubMed (1) [See all records that cite this PMID]	ClinGen Inherited Cardiomyopathy Expert Panel,	SCV000564424.2

Assertion Criteria: The specified variant pathogenicity assertion criteria used for the interpretation of a variant is made publicly available via the ClinVar variant webpage for each variant and the ClinGen evidence repository hosted on ClinGen's website, www.clinicalgenome.org.

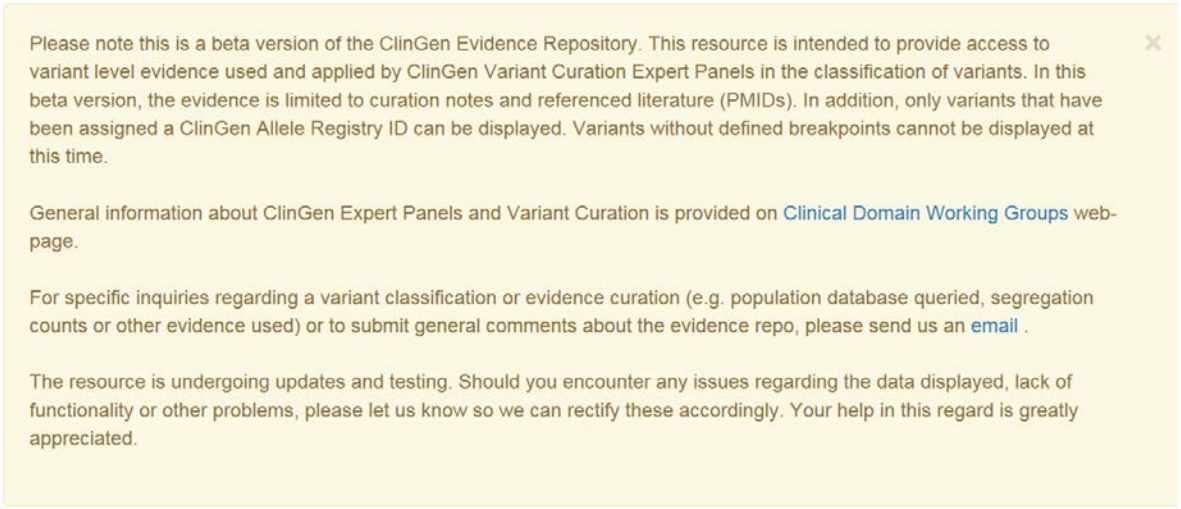
An in-depth explanation of the development and validation of the assertion criteria is publicly available on the specific VCEP page hosted on the ClinGen's website, www.clinicalgenome.org. The information on the VCEP page includes listing of VCEP leaders and coordinators including contact information, full listing of current membership and their employment affiliations, an outline of assertion criteria development and validation, and a hyperlink to a summary table of the assertion criteria developed by the VCEP.

Summary of Assertion and Curated Evidence. A summary of the evidence evaluated, and criteria applied to classify a variant is provided for each final pathogenicity assertion when submitted to ClinVar. The summary includes at a minimum: a list of the specific variant interpretation criteria applied based on the underlying disease-specified ACMG/AMP clinical interpretation guidelines as well as the source of the evidence to apply those criteria. The following is an example of the evidence summary provided in the summary evidence tab in ClinVar:

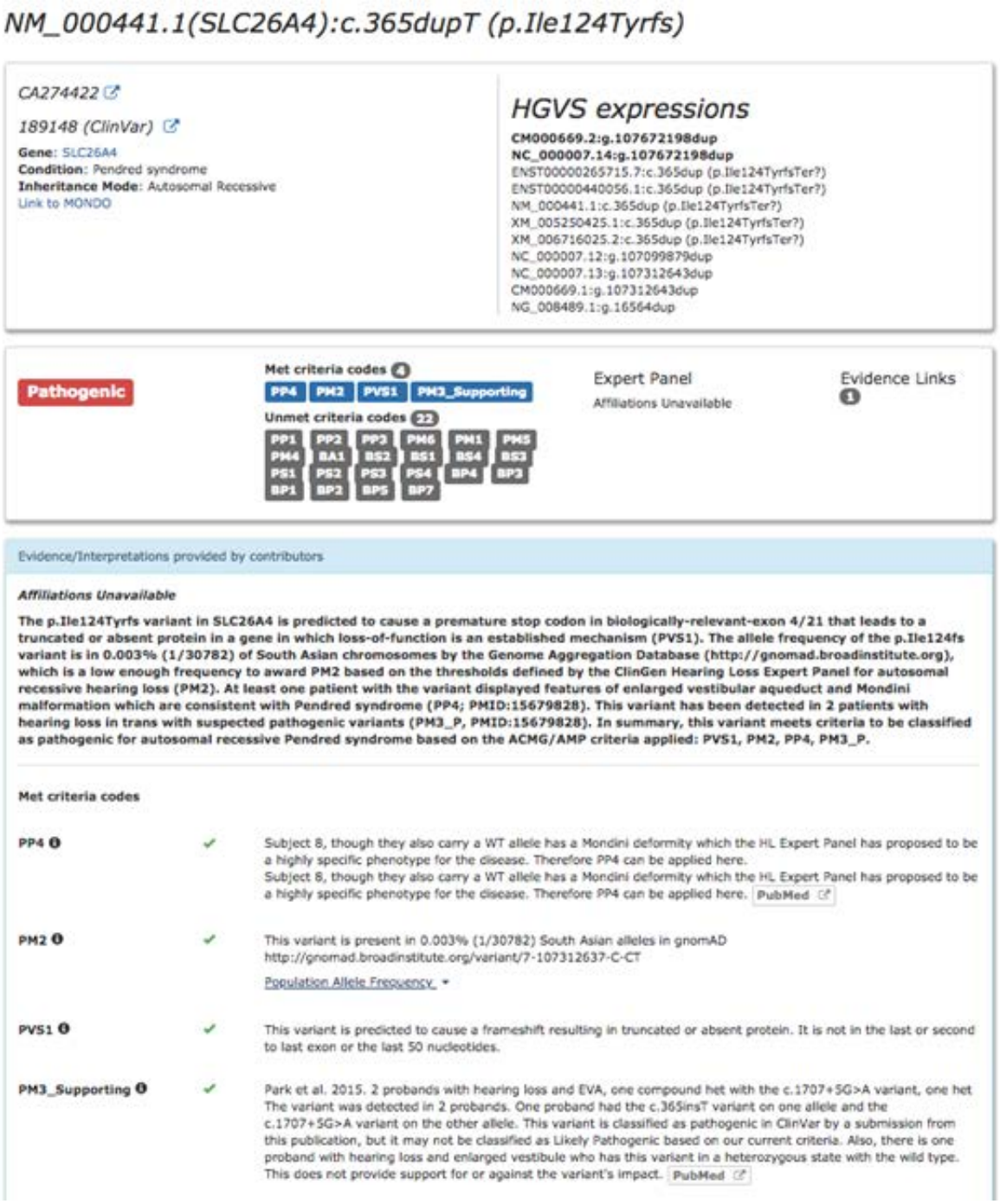
"The c.2167C>T (p.Arg723Cys) variant in MYH7 has been reported in >20 individuals with hypertrophic cardiomyopathy (PS4; PMID:1430197; PMID:27532257; PMID:9829907; PMID:16199542; PMID:20359594; PMID:12707239; ClinVar SCV000059423.5; ClinVar SCV000212630.1). Five of these probands carried additional variants in sarcomere genes (BP2; PMID:20359594; PMID:12707239;ClinVar SCV000059423.5). This variant has been identified as a de novo occurrence in 1 proband with hypertrophic cardiomyopathy (PM6; PMID:1430197). This variant segregated with disease in 7 affected individuals (PP1_Strong; PMID:9829907; ClinVar SCV000059423.5; ClinVar SCV000212630.1). This variant was identified in 2/66738 European chromosomes (PM2; http://exac.broadinstitute.org). This variant lies in the head region of the protein (aa 181-937) and missense variants in this region are statistically more likely to be disease-associated (PM1; PMID:27532257). Computational prediction tools and conservation analysis suggest that this variant may impact the protein (PP3). A different pathogenic missense variant has been previously identified at this codon which may indicate that this residue is critical to the function of the protein (PM5; c.2167C>G p.Arg723Gly - ClinVar Variation ID 42885). In summary, this variant meets criteria to be classified as pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner. The benign evidence code BP2 was not considered to be in conflict with this conclusion given that presence of a second variant can be seen in individuals with cardiomyopathy and may contribute to the severity of disease. MYH7-specific ACMG/AMP criteria applied (PMID:29300372): PS4; PP1_ Strong; PM1; PM2; PM5; PM6; PP3; BP2.

ClinGen Evidence Repository

ClinGen hosts a public interface to facilitate full transparency into the evidence curated and assessed for each variant assertion. The interface is called the Evidence Repository and is hosted as a resource on ClinGen's website, www.clinicalgenome.org. At the time of FDA review of the database, a beta version was provided for review. The Evidence Repository includes the final assertion, the name of the gene and variant using standard nomenclature, a list of the criteria/rules that were met, a summary of the evidence that supports the rules that were met, links to published literature of case-level data, and a hyperlink to the rules developed by the VCEP that made the final assertion. ClinGen includes a link indicating that additional information on the evidence supporting the classification can be requested as depicted below.



ClinGen will enhance the capabilities of the evidence repository to include clickable links to the evidence sources such as population databases and segregation data. In the enhance version, for each variant assertion, the evidence repository will include the final assertion, the criteria met and not met, the same evidence summary provided in ClinVar and additional information on the criteria met codes such as population frequency, segregation data, and hyperlinks to PubMed of published case-level data as depicted in the example below.



Curated Evidence. The evidence assessed to make a pathogenicity assertion is stored within the ClinGen Variant Curation Interface (VCI), described above. The VCI software is open source software developed by ClinGen. Access to versioned, curated evidence in the VCI is available on request directly through the VCEP group leader and/or coordinator or through individual password request.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes that the ClinGen Expert Curated Human Variant Data is transparent and publicly accessible, allowing the public to understand the criteria and processes used to collect and evaluate evidence about variants.

D. *Standard Operating Procedure (SOP) Version Control*

All SOPs that govern processes for how expert panels are developed and approved by ClinGen as well as how variant information is aggregated, curated, and evaluated are made publicly available in their current version on the ClinGen website at www.clinicalgenome.org. Changes are documented and prior versions are made available via request to the VCEP contact.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes that ClinGen oversight and governance procedures are intended for the ClinGen Expert Curated Human Variant Data operations to keep pace with advances in technology and scientific knowledge.

E. *Data Preservation*

All data connected to variants within the ClinGen Expert Curated Human Variant Data, including the variant-specific assertion of pathogenicity, supporting evidence summary, assertion criteria used, ClinGen Allele Registry identifier, and VCEP group responsible are publicly available via ClinVar. As a NCBI maintained archival database for human variants, ClinVar, represents a stable public repository designed for data preservation. All data is backed up within the ClinVar repository database nightly and kept in short-term storage for 60 days.

The VCI is backed up nightly on Amazon Web Services where unique variant IDs and internal checks are performed to ensure accurate data are stored on the back-up files.

Since evidence sources used for variant evaluation are from secondary databases, ClinGen proactively monitors for changes to the secondary databases at defined frequencies that are consistent with the expected change frequency of each secondary database. ClinGen describes the process by which VCEPs must evaluate and validate changes to secondary databases for previously curated variants in the publicly available ClinGen Variant Curation Expert Panel (VCEP) Protocol.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes the ClinGen oversight and governance procedures are designed to maintain stability and architecture of the ClinGen Expert Curated Human Variant Data which includes that all data linkages are maintained. Furthermore, FDA concludes that ClinGen's backup procedures are designed to allow the ClinGen Expert Curated Human Variant Data to be reinstated as necessary.

F. *Security and Privacy*

Personal/protected health information is not connected or maintained within the VCI or attached to variants contained within the ClinGen Expert Curated Human Variant Data and therefore, protected health information is not part of the variant assertion. Documentation of HIPAA training as required by each VCEP member's home institution is maintained by the VCEP coordinator.

All coordinators and members of each VCEP receive training on the use of the VCI. This training includes the policy that only data stripped of any possible protected health information will be entered in the VCI. Any and all evidence curated and reviewed as part of the assessment process is collected from current published sources (e.g. PubMed scientific articles or online public research databases such as Leiden Online Variant Database) or from de-identified clinical lab databases which are required to meet federal HIPAA laws.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes that ClinGen oversight and governance procedures are designed to ensure the protection of privacy of personally identifiable information and protected health information and provide appropriate training for database staff.

G. *Data formats and nomenclature*

Standard nomenclature is used across all processes of the variant curation, assessment and publication of final assertion.

The ClinGen Expert Curated Human Variant Data, and assertions made available in ClinVar and on ClinGen's website, must meet the following standard nomenclature formats: Human Genome Variation Society (HGVS) nomenclature for variants including a reference transcript (RefSeq ID) and/or genomic coordinates according to GRCh37 or GRCh38 reference assemblies, HUGO gene name (HGNC gene symbol), associated condition names using MedGen terms (ClinGen uses Monarch Disease Ontology (MONDO) IDs which are then mapped to MedGen terms), standard ACMG/AMP recommended classification terms.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes that ClinGen oversight and governance procedures are designed to ensure that the ClinGen Expert Curated Human Variant Data uses consistent nomenclature that is widely accepted by the genomics community and makes this information available to users so they can accurately understand the information presented.

H. *Metadata*

Metadata for variant curation are hosted in the VCI, described above. The evidence sources used for variant curation in the VCI are described in the publicly available ClinGen Variant Curation Expert Panel (VCEP) Protocol and made publicly available through requested access to the VCI.

Evidence categories and example sources are described below. Information on each example evidence source is described in Richards et al.

- Population-based data (e.g. allele frequencies in various populations)
    - gnomAD, ExAC, PAGE, 1000 Genomes, Exome Sequencing Project and curated literature
- In silico prediction model data (e.g. evolutionary conservation, splicing predictors)
    - REVEL, SIFT, PolyPhen2, LRT, FATHMN, CADD, phyloP100way, GERP++, MaxEntScan, NNSPLICE
- Experimental data (e.g. animal model, tissue expression)
    - Curated literature for functional domain and experimental evidence
- Case-level data
    - Curated literature for case-control, healthy population observations

    - Curated literature for segregation, cis-/trans-, de novo, and phenotypic specificity
    - Curated non-published clinical data from diseased individuals (e.g. from laboratory testing)
- Gene-centric clinical validity data
    - ExAC constraint scores
    - Links to gene resources such as HGNC, Entrez Gene, Ensembl, UniProtKB and ClinVar

Population, in-silico, and gene-centric evidence is aggregated and displayed for biocurators, and users who request access to the VCI. Experimental and case-level evidence is manually curated and entered by the biocurator from published literature and the other sources described.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes that metadata for ClinGen Expert Curated Human Variant Data are typical for the type of variants within the scope described above and include variant characteristics such as population frequency, patient ethnicity, where available, and segregation data. The evidence source(s) used to support variant assertions are transparently documented as described in Section C. above.

I. *Data Uniqueness*

Unique variant-identifiers are supported through several measures: (1) ClinGen Allele Registry identifier, (2) Variant Curation Interface record, and (3) ClinVar submission accession number (SCV).

ClinGen Allele Registry. Each specific human genomic sequence variant is required to have a unique variant identifier. In addition, every variant will be assigned a canonical identifier by the ClinGen Allele Registry. If a variant has both identifiers, the two will be in one-to-one correspondence and they will be cross-referenced by the two sources. Canonical identifiers are based on sequence alignment against genomic and transcript references. The Registry provides unique variant identifiers both programmatically and via a publicly accessible interface on ClinGen's website.

Variant Curation Interface (VCI) Record. The VCI creates a unique variant interpretation record based on the Allele Registry identifier and, as appropriate, the disease/condition name. Once a variant assertion has been submitted to ClinVar, the resulting ClinVar accession number (ClinVar Submission Record or SCV number) is then linked to the VCI record through the unique identifier for the approved interpretation. This link assures that any future revisions to an assertion will be linked to the public assertion in ClinVar.

ClinVar Submission Record (SCV). Upon submission to ClinVar, each variant-level record will be assigned an accession number of the format SCV000000000.0. If a VCEP includes data from a separate ClinVar submitter to support a variant assertion, the SCV number is noted to prevent future redundant use of the same evidence. This notation occurs within the supporting evidence summary that accompanies the variant assertion and will be included in the VCI within the case-level data for that variant record.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes that ClinGen's oversight and governance procedures for data uniqueness provide

reasonable assurance that individual data points are not represented more than once in the ClinGen Expert Curated Human Variant Data.

J. *Professional Training*

ClinGen VCEPs are expected to represent the diversity of expertise in the field, including all major areas of expertise (clinical, diagnostic laboratory, and research). Membership should include representation from three or more institutions and will encompass disease/gene expert members as well as biocurators.

Biocurators do not have to be gene/disease experts and will be primarily responsible for assembling the available evidence for subsequent expert member review.

Biocurator Proficiency Training

Each VCEP is responsible for coordinating and monitoring training and proficiency of their biocurators in procuring the appropriate data, assessing the data in the context of variant interpretation, and entering the data with sufficient detail into the VCI. New biocurators and/or those biocurators deemed by the VCEP to require additional training are paired with an experienced VCEP biocurator who can teach the relevant skills as they go through the variant interpretation process together.

To facilitate the training process, ClinGen provides general training materials for variant interpretation to new biocurators and newly forming VCEPs, and each VCEP may provide additional training specific to the gene(s) evaluated within the VCEP. Biocurators are expected to join the ClinGen Biocurator working group. This group provides a forum for training and education of all ClinGen biocurators. The Biocurator Working Group has a mechanism for disseminating updates, such as new guidance from the SVI, to ensure that biocurators stay current with ClinGen best practices. A help document on how to use the Variant Curation Interface is available to all biocurators. Biocurators new to the VCI can gain experience by doing practice curations in the VCI as a trainee delegate.

After the training period, the proficiency of the biocurator is evaluated by the VCEP. For example, a biocurator might be asked to independently collect the relevant data and interpret a variant in the VCI. VCEPs may develop a training set of variants for this purpose or may compare the new biocurator's assessment with that of an experienced VCEP member. Once a biocurator has achieved proficiency, this is documented by the VCEP coordinator. Importantly, all variant interpretations are reviewed by the full VCEP membership including non-biocurator, clinical or disease experts prior to being approved.

HIPAA Training

All members are responsible for obtaining HIPAA and human subjects training based on their home institutional/affiliation guidelines and the level of access to human subject data. VCEP leadership and coordinators ensure that members do not inadvertently share data that has not been stripped of protected health information or other identifiers.

Sequence Variant Interpretation Education and Training

The SVI work group provides ClinGen-wide guidance for the process of human variant evaluation to facilitate harmonization of approaches across VCEPs. This guidance is formally presented at regular workgroup meetings via conference calls and published in peer reviewed literature.

SVI educational documents are publicly available on their ClinGen website,

www.clinicalgenome.org. Topically focused presentations are available on request.

All VCEPs receive VCEP-specific training and education that includes the following topics:

- ACMG/AMP criteria for variant interpretation
- ACMG/AMP criteria specification process, including education about which criteria are appropriate for a disease/gene-specific optimization process (e,g., establishment of allele frequency cut-offs)
- Variant curation and use of the VCI

VCI representatives provide one-on-one training regarding the use of the VCI for variant curation. Additional VCI training documents are publicly available for reference. Release descriptions of changes to the VCI software are versioned and are made publicly available. Curation activities within the VCI are guided by the VCI Curation Help documents that are made publicly available.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes that ClinGen's oversight and governance procedures provide assurance that professionals involved in variant evaluation and classification are adequately trained and there are procedures in place to ensure that the individuals meet and maintain high quality standards over time.

K. *Conflicts of Interest*

Expert Panels are expected to represent the diversity of expertise in the field and should be composed of a sufficient number of eligible expert reviewers to address academic and financial conflicts of interest that may arise. ClinGen maintains the following processes with regard to conflicts of interest:

- Academic COI: Authors of literature about relevant variants may serve on the Expert Panel and are welcome to voice their opinion but should not be the major arbiter of a variant classification when there is limited data available and it was provided by that individual or the individual's lab group.
- Financial COI: Commercial entities may participate on the Expert Panel but should not be the major arbiter of a variant classification when there is limited data available and it was provided by that entity.
- No special measures are needed if there is group consensus on a variant classification; however, if a vote is needed, those with relevant conflicts of interest should recuse themselves.
- All conflicts are declared publicly on the www.clinicalgenome.org website and reported in
  publications as appropriate.

Based upon review of the information provided by ClinGen and summarized above, FDA concludes that ClinGen's oversight and governance procedures provide assurance that effort is made to minimize, and make transparent, any potential conflicts of interest that could introduce bias in variant assertions in the ClinGen Expert Curated Human Variant Data.

Discussion of the Evidence to Support Recognition

ClinGen's oversight and governance procedures, which includes VCEP-specific protocols for variant

evaluation and classification for a single gene or group of genes or a particular condition or group of conditions, demonstrate the ClinGen Expert Curated Human Variant Data operates in a manner that provides sufficient information and assurances regarding the source data and its evidence review and variant assertions, providea transparency regarding its data sources and its operations, and contains genetic variant information generated by validated methods. These procedures are sufficiently robust to provide a high degree of confidence that the assertions made using the procedures regarding genotype-phenotype associations are accurate and assurance that assertions from the ClinGen Expert Curated Human Variant Data constitute valid scientific evidence that can be used to support clinical validity of genetic tests in future premarket submissions. These procedures also collect, store, and report data and conclusions in compliance with all applicable requirements regarding protected health information, patient privacy, research subject protections, and data security.

Conclusions

ClinGen oversight and governance procedures, and VCEP-specific protocols for variant evaluation and classification, provide assurance that assertions from the ClinGen Expert Curated Human Variant Data constitute valid scientific evidence and support recognition of the ClinGen Expert Curated Human Variant Data for germline variants for hereditary disease where there is a high likelihood that the disease or condition will materialize given a deleterious variant (i.e., high penetrance) that can be used to support clinical validity of genetic tests in future premarket submissions.