

Genetic Database Recognition Package Cover Sheet

Date: October 30th 2018

Subject: **Supplement to Genetic Database Recognition Request**

Genetic Database Recognition Request

Genetic Database Recognition Tracking Record Number: **Q181150**

Attention: **Brittany Schuck, Ph.D.**

Division of Chemistry and Toxicology Devices

Submission Type: **Q-SUBMISSION: INFORMATIONAL MEETING**

A supplement to Q-SUBMISSION Number: **Q181150**

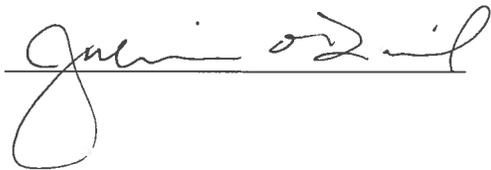
The Clinical Genome Resource consortia, ClinGen, requests recognition through the Genetic Database Recognition program for the ClinGen Expert Curated Human Variant Database as outlined in the prior application and enclosed supplemental materials. The ClinGen database variant classifications and the processes to support them encompass germline variants for hereditary diseases. We request recognition for the full dataset of human variant classifications asserted by ClinGen approved Variant Curation Expert Panels.

The point of contact for this submission is the ClinGen database coordinator.

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Submitted on behalf of ClinGen.

The submitter, Julianne O'Daniel, believes, to the best of his or her knowledge, that all information submitted are truthful and accurate and that no material fact has been omitted.



A handwritten signature in black ink, appearing to read "Julianne O'Daniel", is written over a horizontal line.

Supplement to Q181150 – ClinGen Expert Curated Human Variant Database
Point-by-point Response to FDA Letter of September 21, 2018

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1. Public accessibility and transparency of evidence that supports variant classifications

In a teleconference on September 4, 2018, you indicated that you are currently developing a user-friendly searchable “evidence repository” to publicly display on the ClinGen website the evidence evaluated for each variant classification (also referred to as a variant assertion). You have indicated that you are also developing evidence summaries that will be provided for each variant in the summary evidence tab on the ClinVar website to summarize the evidence that supports each variant classification. While we have discussed how these resources can be implemented to demonstrate public accessibility to and transparency of the variant evaluation process, you have not yet provided information to demonstrate implementation of these resources. To resolve this, please provide information (i.e., links to the searchable evidence repository on ClinGen’s website and evidence summaries on the ClinVar website) that demonstrates implementation of the resources you are developing. As 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*”, and our email dated July 17, 2018, and further discussed during our teleconferences on August 14, 2018 and August 29, 2018, evidence used to support variant assertions (i.e., classifications) should be clearly and transparently documented for the public and made in language that is clear and understandable. This should allow users to understand how the variant classification was made, and what evidence sources underlie that classification. In your response to this letter, please make sure the information you provide to demonstrate implementation of the searchable evidence repository on the ClinGen website and evidence summaries on the ClinVar website supports that the evidence underlying each variant classification is publicly accessible and transparent, and presented in a language that is clear and understandable.

Response to item 1

As described, we have implemented a new requirement to include a descriptive summary of the evidence supporting all finalized variant classifications as submitted to ClinVar. These have now been completed for the 5 currently ClinGen approved Variant Curation Expert Panels (VCEPs): MYH7, RASopathy, Hearing Loss, PAH and PTEN. These can be reviewed by visiting the ClinVar Submitter page and following the links to the ClinGen Expert panels or by clicking below:

Currently displayed in ClinVar

ClinGen Hearing Loss VCEP: <https://www.ncbi.nlm.nih.gov/clinvar/submitters/506744/>

ClinGen PTEN VCEP: <https://www.ncbi.nlm.nih.gov/clinvar/submitters/506694/>

Submitted to ClinVar – awaiting post

ClinGen PAH VCEP: XXX

Awaiting resubmission to ClinVar

ClinGen RASopathy VCEP: <https://www.ncbi.nlm.nih.gov/clinvar/submitters/506439/>

ClinGen Inherited Cardiomyopathy VCEP:
<https://www.ncbi.nlm.nih.gov/clinvar/submitters/506161/>

In addition, a public interface has been developed to facilitate full transparency into the evidence curated and assessed for each of the finalized variant classifications published in ClinVar. The interface is currently called the Evidence Repository. The beta version of this web-based access is available for review and comment at: <https://erepo.clinicalgenome.org/>

As discussed on September 10, 2018, please also address the following:

1.a. As discussed during our teleconferences on August 14, 2018 and August 29, 2018, please make sure that filtering allele frequency (filtering AF) and allele frequency are well-defined and clearly indicated for each expert panel since it appears that each expert panel chooses to use either filtering AF or allele frequency to evaluate population frequency. That is, the type of allele frequency that is used for each expert panel differs, so this should be clearly indicated in the evidence summaries in ClinVar and searchable evidence repository on ClinGen's website.

Response to bullet a

Allele frequency refers to the number of times an allele has been reported within a population. Filtering based on allele frequency may sometimes be done to define variants that are above a threshold and thus 'too common' to be pathogenic for a rare Mendelian disorder. The Richards et al. guidelines reference allele frequency in the following ways:

- PM2 Absent from controls (or at extremely low frequency if recessive) (Table 6) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium
- BA1 Allele frequency is >5% in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium
- BS1 Allele frequency is greater than expected for disorder

The BA1 and BS1 criteria may be specified by a VCEP in accordance with the particular gene-disease. These modifications are indicated in their public specified rules. When a variant has been classified solely on the application of specified allele frequency for Benign/Likely Benign, (used as a standalone criteria) this will be described in the evidence summary.

Further, the source data for the allele frequency used in a VCEP variant assessment should be available for review along with other curated evidence in the Evidence Repository.

1.b. In the information you provided during interactive review, abbreviations and symbols were not well-defined. For example, the '-' symbol was used in the MYH7 spreadsheet to indicate that the variant was absent from the population frequency database, but was not defined within the spreadsheet. As discussed during our teleconferences on August 14, 2018 and August 29, 2018, please make sure that if any abbreviations and symbols are used in the searchable evidence repository on ClinGen's website and the evidence summaries in ClinVar, they are defined.

Response to bullet b

These symbols would only be present within VCEP notes or in tables prepared for publications. We will certainly make the recommendation for VCEPs to be mindful of this in publications. These symbols are not applicable for the searchable Evidence Repository or for the ClinVar evidence summaries.

1.c. It is our understanding that the searchable evidence repository that will be made available on the ClinGen website, clinicalgenome.org, will be very similar to the variant curation interface (VCI) for

which we had access during our review. We agree that all evidence sources used in variant evaluation should be publicly accessible and transparent, so please make sure that each evidence source that was used in the evaluation of each variant classification is also included in the searchable evidence repository. For example, population frequency information for all ethnicities, computational prediction models that support the classification, case-level data, and all segregation data should be made available.

Response to bullet c

The curated/reviewed evidence in the VCI will be used to populate the Evidence Repository. In addition, all curation notes that describe the assessment of evidence and any reasoning given for why a criterion was Met or Not Met will also be displayed.

1.d. To ensure that all evidence sources used during variant evaluation are transparent and can be easily accessed by the public, please make sure the searchable evidence repository has the same clickable links to the population databases and computational predictor tools that are contained within the VCI. Alternatively, please clearly describe each evidence source used in your standard operating procedures (SOP(s)), that will be publicly available.

Response to bullet d

Within the Evidence Repository, when the evidence displayed is curated from an external source, the link to that source has been embedded where ever possible. Further, as the Evidence Repository is intended to display curated evidence fields from the VCI, it will be kept current with evidence sources as utilized by the VCI.

The general description of evidence sources and explanations is included in the VCEP Protocol document p. 9-11. As the list of evidence sources is a potentially dynamic list, the current list and corresponding reference links have been incorporated into the Variant Curation SOP on pages 26-28 of the v1 draft. The v1 draft of this document is included with this supplement. Both of these documents will be posted on the ClinGen webpages for public access.

1.e. As discussed in our teleconference on August 29, 2018, the publication, “*Adaptation and validation of the ACMG/AMP variant classification framework for MYH7-associated inherited cardiomyopathies: recommendations by ClinGen’s Inherited Cardiomyopathy Expert Panel*”, that you provided to support the variant evaluation SOP for the Inherited Cardiomyopathy (MYH7) Variant Curation Expert Panel (VCEP) indicated that the VCEP used clinical judgement to “upgrade” the rule-based classification for several variants. That is, the VCEP determined that although the combining criteria used by ACMG and the VCEP indicated a specific classification/pathogenicity, the VCEP used their clinical expertise in the oversight of the curation and assertion processes to modify the classification/pathogenicity. During our call on August 29, 2018, you confirmed that each VCEP uses the ACMG combining criteria to make a pathogenicity classification using the ACMG rule-based criteria developed by the VCEPs. Although we understand that VCEPs can use their expertise and oversight to make a change to the final classification, as discussed, the variants for which this was done was not clearly described in the summary spreadsheets provided for review or in a manner that is publicly accessible or transparent. Furthermore, based on our review of the evidence summary spreadsheet (*MYH7 variant evidence suppl from gim2017218x7.xls*) provided for the Inherited Cardiomyopathy VCEP, it appears there is a discrepancy for MYH7 c.4377G>T (p.Lys1459Asn), ClinVar Variant ID 43012, between the criteria met (PP3 and BS1) and the final

classification (likely benign), that was not described within the evidence summary. For any variant where the VCEP has made a change to the rule-based classification (i.e., did not follow the combining criteria as described by ACMG and implemented by the VCEP), please make sure that the change is clearly described in the user friendly searchable evidence repository on ClinGen's website and evidence summaries in ClinVar. For example, in the searchable evidence repository where you indicate the VCEP final classification, you could include a clarifying statement to indicate the original classification and the rationale for the change. For the evidence summary in ClinVar, you could summarize the classification with the pathogenicity that would have been made with the ACMG combining criteria, the VCEP pathogenicity and a brief rationale that supported the VCEP's change. This is important to facilitate outside users' review and understanding of the process used for variant evaluation and classification. Please make sure this is completed for all expert panels, and that the expectation for VCEPs to include this type of information is included in your SOP for variant evaluation and assertions used by VCEPs.

Response to bullet e

Guidance to this effect has been added to the VCEP Protocol document in item 2.2.A. and 3.1.D. An updated version of this document has been included with the supplement. In particular, in section 2.2.A (page 8) the combining criteria from Richards et al. are described and examples are given when they may be modified/specified. Later in 3.1.D. (p13-14) a specific bullet addresses the need to highlight exceptions such as when an evidence category is "overruled" so to speak. A detailed example of how to include this in an evidence summary statement is given on p 14 of the VCEP Protocol.

1.f. As discussed during our teleconference on September 10, 2018, the evidence summary spreadsheets (*RASopathyEPVariantsPhaseI*, *RASopathy_suppl from gim20183x3.xls*, and *RASopathy_Noonan_VariantTrail_Phase2_alllabs_final.xls*) provided for RASopathy contained information that appears to be contradictory within the spreadsheets or between the spreadsheets and the information in ClinVar. For example, the *RASopathy_suppl from gim20183x3* spreadsheet indicated that the RASopathy EP variant classification for PTPN11c.794G>A(p.Arg265Gln) (ClinVar Variant ID 40522) was pathogenic while the expert panel final results section in *RASopathy_Noonan_VariantTrial_Phase2_alllabs_final* indicates that the variant should be classified as VUS due to "conflicting phenotypic data=keep as VUS despite de novo events." Furthermore, for MAP2K2c.784G>A(p.Val262Ile) (ClinVar Variant ID 46242), *RASopathy_Noonan_VariantTrial_Phase2_alllabs_final* indicates that curated evidence supports that criteria PP2 and BP4 were met; however, *RASopathy_suppl from gim20183x3* (and ClinVar) indicates that only BP4 was met. In the searchable evidence repository on the ClinGen website, and the evidence summaries provided in ClinVar, please make sure that the information in each resource is accurate with respect to the final assertion made by the VCEP and that all criteria that were determined to be met are accurate and provided transparently.

Response to bullet f

In an effort to quickly provide insight into the evidence curated, the spreadsheets provided for RASopathy contained notes regarding the evidence that did not represent the final assessment and classification. RASopathy is one of the earliest VCEPs and therefore was not initially curated and reviewed within the VCI. This led to the accumulation of several different variant spreadsheets - some were quite large and included all the evidence and others were more limited as they were used to capture the actual discussion and final assessment. The VCI has streamlined this process

such that the evidence and discussion can be captured in one database. The evidence summaries within ClinVar and the evidence with supporting statements as displayed within the Evidence Repository will only include the final assessments and classification as approved by the VCEP thereby eliminating the potential confusion you reference in this point.

2. Scope of recognition request

You have provided information on ClinGen’s process for evaluating and approving VCEPs and information to demonstrate the acceptability and robustness of this process for three VCEPs, Inherited Cardiomyopathy, RASopathy, and PAH. You have indicated that you are seeking database recognition for the “full dataset of germline variant classifications” for hereditary disease that would include variants classified by additional VCEPs (i.e., beyond the three provided in your submission). You have not provided any information on the additional expert panels that you propose may be included in the ClinGen database, or criteria for how you will determine whether or not the VCEP falls within the scope of the recognition should the FDA make a decision to recognize the ClinGen database for the proposed scope. So that we can determine whether or not recognition for the broad scope of “germline variants for hereditary disease” can be supported by the information provided for the three VCEPs we have reviewed, please provide the criteria by which you will evaluate VCEPs for meeting your definition of “germline variants for hereditary diseases” if the ClinGen databases is recognized for this broader scope. It is our understanding, and FDA’s expectation, that in the scenario that FDA recognizes the broader scope, ClinGen will have the same type of information (e.g., SOPs are publicly available, VCEPs would follow the same protocols for development and validation of modified ACMG rules, evidence summaries are provided in ClinGen and the evidence supporting each variant classification is in the searchable repository on ClinGen’s website, etc.) that was provided for our review for each additional VCEP.

Response to item 2

We are requesting recognition of all finalized, approved variant classifications made by ClinGen approved VCEPs. Currently, this would include variant classifications from five approved VCEPs: MYH7, RASopathy, PAH, PTEN and Hearing Loss. In order to be a ClinGen VCEP, the group must adhere to ClinGen processes, obtaining step-wise approval, as outlined in the VCEP Protocol document for development, rules specification, piloting testing and validation as well as abide by on-going curation, assessment and re-analysis. Please refer to the ClinGen Clinical Domain Working Group status and progress webpage for insight into current VCEPs in the ClinGen development stage. Please note that Variant and Gene curation groups are listed. Only Variant Curation Expert Panels classify variants and therefore would fall within the scope of this application.

https://www.clinicalgenome.org/working-groups/groups/#curation_section_8786

3. Changes to secondary databases used as evidence sources by ClinGen Database

You provided your SOP, *ClinGen Response (08.06) Changes to external data sources.docx*, which describes your assessment of changes to secondary databases used as evidence sources by the ClinGen database. As indicated in our email on September 4, 2018, you have not provided sufficiently detailed information on the timeframe for this process nor clearly defined the process for validating variants following changes made to the secondary databases to ensure that changes that may impact the variant classifications are evaluated and addressed in a timely manner. As discussed

during our teleconferences on September 4, 2018 and September 10, 2018, since you are working to develop your resources to address item #1, you have not yet provided a response to our requests communicated via email on September 4, 2018. To resolve this, in your response to this letter, please make sure you address all comments communicated via email on September 4, 2018, which includes clarifying how many variants are evaluated during validation of a secondary database change and including in your SOP the timeframe for the evaluation and validation process. That is, please clearly define the timeframe for evaluating previously curated variants by the VCI developers and curators, the timeframe for notifying the VCEP of changes, and the timeframe for the VCEPs evaluation of the impact to their specific variants. In your response, please also confirm that this SOP will be made publicly available on the ClinGen website.

Response to item 3

The VCI User group is responsible for defining the evidence sources utilized by the VCI. The VCI User group is composed of representatives from the Sequence Variant Interpretation (SVI) working group, the Biocurator's Working group, the Data Model working group, the ClinGen Steering Committee, and the Clinical Domain working group (CDWG) Oversight Committee. Therefore, the VCI User group would direct the VCI developers regarding any necessary changes or updates to the external secondary data sources.

The VCI User group have taken steps to ensure the ability to proactively monitor the field for changes to external data sources. These steps include attendance at annual professional education conferences for human genetics (ASHG, ACMG, ESHG, CCG, etc). These meetings are spaced throughout the year such that at least one conference occurs each quarter. Attendance at these conferences enables the VCI User group to actively engage and learn about modifications to existing data sources and development of new ones.

In addition, ClinGen and members of the VCI User group, specifically, have developed collaborative relationships with community leaders who develop and maintain these external data sources such as ExAC and gnomAD. We also participate in international collaborations including Global Alliance for Genomic Health (GA4GH) which enable timely awareness of new external data sources and contributions to improve current ones. Thus, we are able to continuously and proactively monitor and contribute to external data sources.

Once aware that a data source has or will be modified, ClinGen will engage with the data source developers to understand the extent and basis of changes. For instance, is the change simply adding more populations in gnomAD, or has the format in which the data are shared changed that could impact ingest into the Variant Curation Interface. This assessment will then determine the extent of validation that will be necessary to ensure that the data can be accurately brought into the VCI and used for curation. More validation will be needed for format changes versus simply adding additional volumes of data. The VCI developers will validated accurate ingest of the data through comparing display of the data in the VCI compared to display in the originating system.

VCEPs and the Biocurator WG will be alerted to the updated or new data source in the VCI along with any education or training as appropriate provided through the SVI and Biocurator WG. VCEPs will then consider their modified rules and what if any impact the new/updated data may have. The SVI will provide assistance as needed. VCEP coordinators and biocurators will examine the new/updated data by review and comparison of prior curated variants and the data that was used for classification. This should be done for a subset of variants (~5-10) selected for possible impact based on specified rules if applicable. The purpose of this review is to familiarize the VCEP with the new/updated data and to ensure that any changes make sense with respect to the changes brought in (e.g. are substantive changes in population frequencies only occurring with new ethnic populations whereas population frequencies in previously well-represented ethnicities are remaining consistent). Higher throughput comparisons can be performed to see if any variants may be impacted by the new/updated data. For example, if a VCEP has set allele frequency thresholds for applying BA1, BS1 and PM2, a script can be run to determine if any changes in the application of these three rules would happen for any approved variants.

This review process enables the VCEP to determine if the new/updated data is anticipated to result in medically significant changes to prior variant classifications. Medically significant is defined as a change between P/LP and VUS/LB/B classifications. Review and reassessment of prior classified variants will proceed in accordance with the Variant Reanalysis and Discrepancy Resolution policy as outlined in the VCEP Protocol document on p. 18-20. If the new/updated data would result in medically significant changes then reassessment should occur within 3 months of notification. Revised classifications would be published to ClinVar within 6 months.

When the data is not expected to result in medically significant changes, the variant reanalysis would follow the routine re-assessment which occurs every 2 years.

The implementation and communication of the change will thus proceed as follows:

- Determination of the type of updates from the data source (data format, content, etc)
- The VCI developers validate ingest of the updated data source to the VCI.
- Curators review the content of the data through checking previously curated variants.
- The VCEP variants are queried to determine which variants, if any, are impacted by the new content and the VCEP is alerted to this.
- The VCI adds the new/modified data source and publishes it via a release update.
- All VCI users, and VCEPs are alerted to the VCI release update.
- VCEPs will review and reassess impacted variants for possible changes to classifications in accordance with reanalysis policy.
- Any changes to classifications will be published via an updated submission to ClinVar and/or published in peer-reviewed journals.

4. ClinGen Database SOP

You provided your SOP, *ClinGen VCEP Dev and Review Process*, that describes VCEP development and implementation requirements, including requirements for membership and training, addressing conflicts of interest, modification of ACMG rules, validation of modified ACMG rules, variant curation and final variant assertion of pathogenicity requirements, expectations for submission of variants to ClinVar, re-evaluation of variant assertion requirements, and the process for receiving inquiries regarding conflicting variant assertions. As indicated via email on September 4, 2018, the provided SOP lacks sufficiently detailed information on the ACMG combining criteria used by each VCEP and the evidence sources used in the variant curation interface. We asked that you provide additional detail within your SOP; however, as discussed during our teleconferences on September 4, 2018 and September 10, 2018, since you are working to develop your resources to address item #1 you have not yet provided a response to our requests. To resolve this, in your response to this letter, please provide your revised SOP that addresses all comments provided via email on September 4, 2018 to ensure that the ClinGen database SOP contains sufficient information to facilitate outside users review of the process (including evidence sources) used in variant evaluation. Also, since you have indicated that each variant will now have an evidence summary in ClinVar, please make sure that your SOP is revised to include the expectations for providing evidence summary information for submission to ClinVar for each expert panel. For example, in your protocol, you could indicate that VCEPs should include a summary of evidence that underlies the variant classification for each variant that will be uploaded to ClinVar. The expectations should clearly describe the format (if standardized) and the minimum amount of information that should be included in the summary. In your response to this letter, please also confirm that the ClinGen expert panel development and process SOP will be publicly accessible on the clinicalgenome.org website.

Response to item 4

The revised VCEP Protocol document has been included with this supplement. Guidance regarding the evidence summaries that must accompany variant classifications is contained in section 3.1.D on pages 13-14.

5. VCI evaluation

You have indicated that the phenylalanine hydroxylase (PAH) VCEP and all future VCEPs will utilize the variant curation interface for variant evaluation. During our review of the PAH variants within the VCI, we identified that criteria that were not marked as “met,” were all denoted as “not evaluated” rather than “not met.” In an email dated September 4, 2018, we requested information on how this may impact the variant assertion since it appeared that instead of being “not evaluated,” criteria should be evaluated and determined to be “not met.” As discussed during our teleconferences on September 4, 2018 and September 10, 2018, since you are continuing to work on your resources to address item #1, you have not yet provided a response to our request. To resolve this, in your response, please address the following which were described in our email on September 4, 2018:

- (Bullet 1) It seems that for some of the criteria that are indicated as “not evaluated,” they should be “not met.” For example, for the population criteria there are three options, BA1, BS2, or PM2. If PM2 is met, it seems the other two should be “not met.” They are currently listed as “not evaluated.” It is our understanding that “not evaluated” is the default and that curators should select “not met” if

the evidence does not support a positive evaluation of the criterion and therefore, it appears that biocurators may not have correctly selected “not met” for some criteria. For future VCEPs, the potential impact of “not evaluated” versus “not met” should be described in training documents for the VCI to avoid confusion and ensure that all evidence is being evaluated, with the appropriate selection being chosen from the drop down menu. Since this should be addressed by the VCEPs to ensure that this does not impact their process of variant evaluation using the VCI, you should clearly describe how the choices in the drop down menu may impact variant classification in your ClinGen VCEP development and review process SOP under section A.2.

Response to item 5, bullet 1

We have planned an update to the VCI which would eliminate the choice “Not Evaluated” as this selection mis-represents the curation and evidence review process. A new default selection would be coded. The wording of this default is to be “Not Applied.” It was felt that “Not Applied” was the most appropriate selection for the instance in which there was no evidence for the given criterion or for which mechanistically the particular criterion did not apply to the variant being assessed (e.g. criterion refers to Loss of Function when the variant is missense).

Until this update can be coded and released in a future VCI software update, guidance regarding the use of Not Met rather than the default Not Evaluated has been disseminated to VCEP coordinators and the Biocuration WG to assist with biocurator training. Guidance has been added to the VCI Help documentation at: <https://github.com/ClinGen/clin coded/wiki/VCI-Curation-Help#2-criteria-evaluation-choices> This will ultimately be addressed in the Variant Curation SOP.

- (Bullet 2) It is unclear how criteria being “not evaluated” may impact the pathogenicity classification since this may impact whether a variant would be classified as a variant of uncertain significance if the not evaluated evidence was contradictory to the evaluated evidence. That is, since variants are classified as uncertain significance if the criteria for benign and pathogenic are contradictory (Table 5, Richards et al), if criteria that are contradictory to the criteria that are met were “not evaluated” but could have been met if they were evaluated, there could be available data/evidence that would suggest a variant should be classified as VUS. However, if there are criteria met to support a classification and all criteria were evaluated and “not met,” there would be no potential for a VUS classification. Please provide information on any ClinGen and VCEP processes (e.g., training of curators, how VCEPs will use the VCI, etc.) that would mitigate any negative impact from the lack of evaluating all possible evidence on the variant classification. For VCEPs that are already using the VCI (i.e., PAH), if certain criteria were not evaluated and therefore, there could be conflicting information that was not evaluated that may change the final assertion, this should be described transparently in your search evidence repository on ClinGen’s website and the evidence summaries in ClinVar. For example, including a disclaimer that some evidence sources were not evaluated for all variants.

Response to item 5, bullet 2

All variant-level evidence is reviewed and thus evaluated to determine if an evidence criterion is “met” or not. If a piece of evidence is “met” but the VCEP chooses not to apply that criteria in the determination of the final classification this would be considered an Exception. Exceptions have been addressed under response to bullet 1e above. The situation you describe from PAH curations in the VCI was due to biocurators leaving criteria in the default “Not Met” label when there was no evidence to consider. The remedy to this situation involves both biocurator training use the

appropriate label as well as a change to the VCI to eliminate the Not Evaluated option. To prevent confusion from external users, the Evidence Repository will not display the criteria labeled as Not Evaluated.

6. Publicly available VCEP documentation

You have indicated that all documentation for the assertion criteria for each VCEP will be publicly available via the VCEP submitter pages housed within the ClinVar domain and on the specific VCEP page within the ClinGen website, clinicalgenome.org. As discussed during our teleconference on August 29, 2018, the RASopathy VCEP has the expert panel documentation clearly displayed and linked to the VCEP submitter page, however, this has not been completed for the Inherited Cardiomyopathy or PAH VCEPs. You indicated during our discussion that the Inherited Cardiomyopathy and PAH VCEP pages would be updated. It appears that this has not yet been resolved. To resolve this, please make sure the assertion criteria (i.e., the tables containing the modified ACMG rules) for each panel are clearly displayed on the VCEP pages within the ClinGen website and on the VCEP submitter pages in ClinVar and provide information to demonstrate that this issue has been resolved in your response to this letter.

Response to item 6

Each ClinGen VCEP has a page on clinicalgenome.org (https://www.clinicalgenome.org/working-groups/groups/#curation_section_8786) and a submitter page at ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/docs/submitter_list/). The specified variant classification criteria are linked to both places. In addition, links have been placed between these two public access points: VCEP submitter pages on ClinVar and the VCEP page on ClinGen.