Batch ClinVar Submission in ClinGen's Variant Curation Interface (VCI)

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Abstract

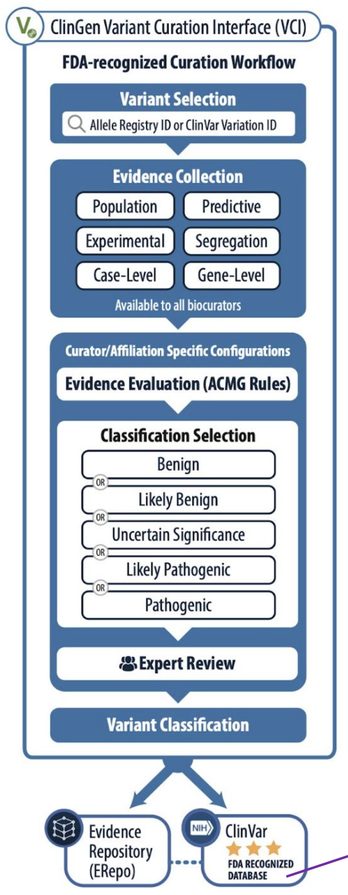
The NIH-funded Clinical Genome Resource Consortium Variant Curation Interface (ClinGen VCI) is a global, open-source variant classification platform for supporting the application of evidence criteria and classification of variants based on the ACMG/AMP sequence variant classification guidelines. To facilitate evidence-based improvements in human variant classification, the VCI is publicly available to the worldwide genomics community. The VCI is among a suite of tools developed by ClinGen, and supports the FDA-recognized human variant curation process of ClinGen Variant Curation Expert Panels (VCEPs). ClinGen is expanding to involve more curators and teams of curators (affiliations) working today as part of an increasing scale of activities that will increase genetic variant curations across a greater number of genes. The variant curation workflow is intended to support dissemination of variant curations into two repositories: the ClinGen Evidence Repository (for approved ClinGen VCEPs) and ClinVar. Support for dissemination of curations into the Evidence Repository from the VCI is an API-driven process via the ClinGen Data Exchange; however, ClinVar submission from the VCI has been largely manual to date.

Here we present the first in a series of planned software features to provide a better ClinVar submission experience for VCI users. This batch submission feature allows users to create an active batch of curated variants and then download a preformatted file of the curation data, which can easily be submitted to ClinVar. This provides a faster process for users submitting variant interpretations to ClinVar. It also allows VCI users to annotate which of their curations have been submitted to ClinVar. Future feature plans for ClinVar submission from the VCI include providing VCI users with real-time feedback on the status of their ClinVar submissions, as well as direct API-based submissions from the VCI. These features together will further streamline workflows for both ClinGen VCEPs and non-ClinGen VCI users, and further the ClinGen goal of creating scalable curation workflows to support the clinical genomics community.

Variant Curation Workflow

Summary of the ClinGen Variant Curation Workflow supported in the VCI

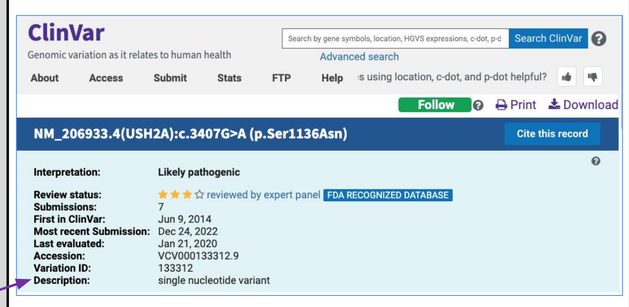
- Biocurators select a variant
- A pool of evidence for that variant is collected (brought in automatically and added manually)
- Biocurators evaluate the evidence based on the ACMG rules
- Based on the overall evaluations a classification is suggested by the VCI
- ClinGen Variant Curation Expert Panels (VCEPs) review all the data to determine a final classification
- Final VCEP classifications are disseminated to public sites:
  - ClinGen Evidence Repository (ERepo)
  - **ClinVar**



ClinVar Submission

ClinVar submissions via the VCI

- ClinGen VCEP classifications via VCI are:
  - automatically provided 3 stars
  - labelled as coming from an FDA-recognized database
- VCI supports VCEPs to generate the data required for ClinVar submissions
- New batch ClinVar submission pipeline developed to support generating ClinVar submission data from the VCI at scale
- Ultimate goal is to support direct submission of batches of classifications from the VCI to ClinVar via their API

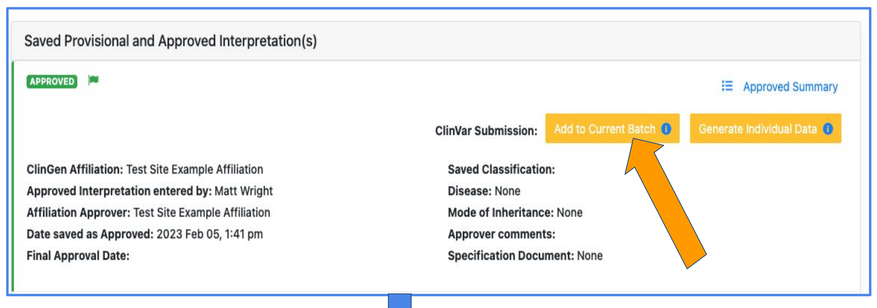


Example of VCEP variant classification submitted to ClinVar. Note the three stars and FDA-Recognized Database label.

Batched ClinVar Submission Workflow in the VCI

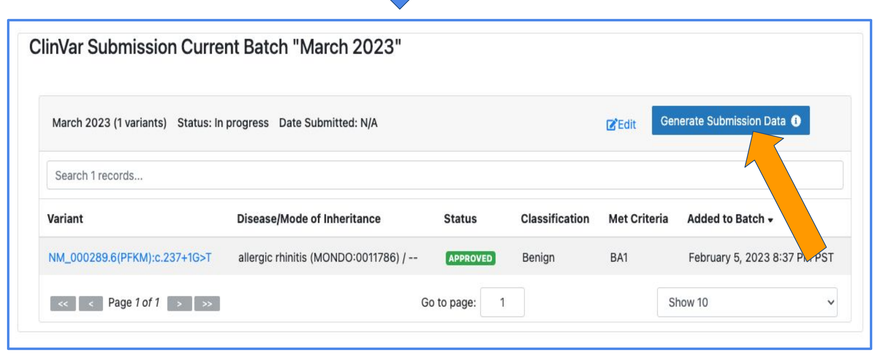
ClinVar Submission Batching

Upon final Approval, each variant Classification can be added to the current batch.



The current batch contains all the classifications added since the previous ClinVar batch submission.

At any time, all the classifications in the current batch can be used to generate submission data.



The VCI does not currently support direct ClinVar submission.

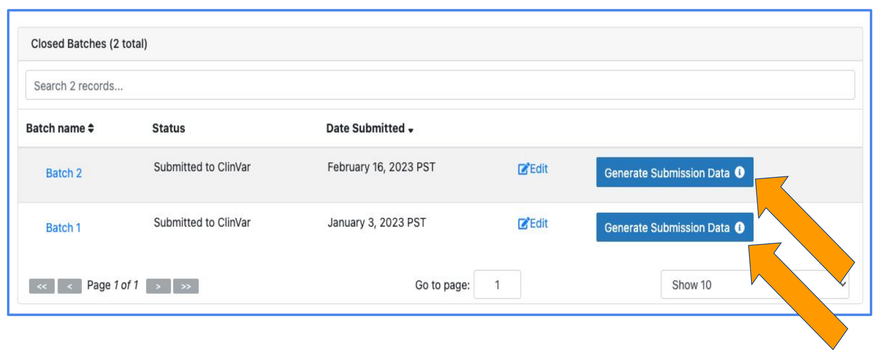
We are working to support direct submission of batches directly from the VCI to ClinVar via their API.

To submit variants to ClinVar, download the ClinVar submission file and submit directly through the ClinVar submission portal.

- For more information on ClinVar submission, contact: **variantcuration@clinicalgenome.org**

Once batches have been submitted to ClinVar, the submission date is recorded and the batch is closed.

Closed batches are saved permanently and the data within them can be accessed again.



Open for Community Use

The VCI is open for ALL variant curators to use

- **ALL** variant curators are welcome to register to use the VCI
  - One third of all VCI users are not associated with ClinGen
- **ALL** variant curation groups can request an affiliation account in the VCI
  - Members of affiliations can curate and classify variants together within the VCI
- **ALL** affiliations can make use of the ClinVar batch submission pipeline
  - Only ClinGen VCEPs automatically get 3 stars with an FDA-recognized label

We welcome you to use the VCI...

How to make use of the VCI

- **REGISTER** to use the VCI by creating an account via the header at:
  curation.clinicalgenome.org
- **TEST** out the VCI functionality on our demo site:
  curation-test.clinicalgenome.org
- **REQUEST AN AFFILIATION** for your team by emailing our help desk:
  vci@clinicalgenome.org
- **VIEW HELP DOCUMENTATION** which describes how to use the VCI:
  vci-gci-docs.clinicalgenome.org
- **VOLUNTEER** as a curator for ClinGen:
  clinicalgenome.org/working-groups/clingen-community-curation-c3

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Questions? Contact us at *vci@clinicalgenome.org*