# ClinGen Gene Tracking System SOP

Purpose: The ClinGen Gene Tracking System provides a centralized database to catalogue all planned, in progress, and completed gene-disease curations, and record evidence supporting lumping/splitting decisions. As such, the Gene Tracking System:

1) Avoids duplication of curator effort,
2) Promotes discussion between groups interested in curating the same gene,
3) Allows for assignment of curators to different genes (for precuration) or gene-disease pairs,
4) Facilitates the precuration process, as defined by the Lumping and Splitting Working Group.

The ClinGen Gene Tracking System is the first step in the gene curation process. **At a minimum, the gene, disease entity, and expert panel must be entered into the Gene Tracking System before starting the gene-disease clinical validity curation in the ClinGen Gene Curation Interface (GCI).** The Gene Tracking System is currently a stand-alone database. In its next phase (under development), it will communicate with the ClinGen Data Exchange, and will allow users to extract relevant data, such as number of curations per GCEP over a specified time period.
Use of the ClinGen Gene Tracking System is restricted to ClinGen affiliated WG and EPs and is not available for public use at this time.

Database Link: To navigate to the ClinGen Gene Tracking System visit https://clingen.sirs.unc.edu

Registration: For newly formed Clinical Domain Working Groups and Curation Expert Panels, the coordinator should contact the ClinGen Gene Curation Interface (GCI) team at clingen-helpdesk@lists.stanford.edu to register the affiliation. Once the affiliation name has been accepted by the GCI team, please email the ClinGen Gene Tracking System administrators at clingentrackerhelp@unc.edu with the approved name of the affiliation, the names and email addresses of each member that will be curating for the group, and the role of each member, either 'Curator' or 'Coordinator' (see "permissions" section below for a description of these roles). ***Note, it is possible to have multiple individuals designated as a 'Coordinator.'***

Permissions: The ClinGen Gene Tracking System permissions are based on the affiliation system employed by the ClinGen Curation Interfaces (GCI and VCI), as well as the user type. The addition of genes to an Expert Panel list and editing of current gene precurations is restricted to the user's affiliation membership(s). Users designated as "Coordinator" have the ability to add genes to the list for their affiliations, edit all genes and precurations under their affiliation(s), change the status of a curation, and assign curators to genes within the Gene Tracking System. The "Coordinator" also has the ability to add new users to their group, and change the permissions for a user within their group by contacting the Gene tracking system administrators. Users classified as "Curator" are restricted to editing the gene(s) and precuration(s) to which they have been assigned. "Curators" can also be designated to allow them to edit all gene records for their affiliation(s); this designation needs to be communicated to the administrators by the "Coordinator." **Note, every user can view the entire gene list, the status of a curation, and precuration information under the "Curations" tab.**

How to use the ClinGen Gene Tracking System:

# For Coordinators:

## 1. Gene Entry

**a.** There are two mechanisms to enter genes of interest. Both of these methods are restricted to users that are designated as 'Coordinators'. Users designated as 'Curator' can only edit their assigned curations:

**i.** Bulk upload

**1.** After logging into the site, from the dropdown menu under your user name, select the "Bulk Upload" option (Figure 1, orange arrow).

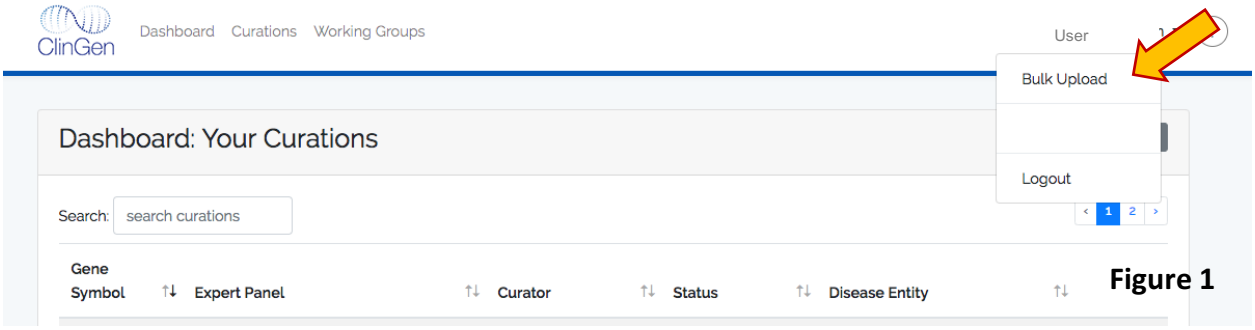



**Figure 1**

**2.** For bulk upload of genes, a downloadable Excel template is provided (Figure 2, orange arrow).

**a.** The minimum required information for a bulk upload is: (1) selection of the relevant Expert Panel, and (2) the HGNC nomenclature for the gene(s).

**b.** Note that alteration of the Excel template, other than entry of the required information, will result in an error message and the inability to upload the gene list.

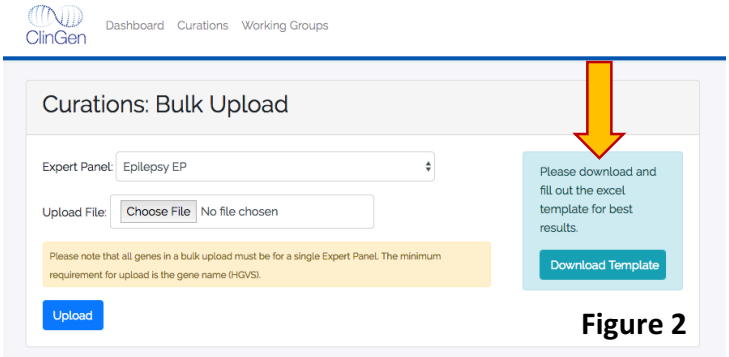



**Figure 2**

ii. Manual Entry

1. For manual entry of a gene(s), use the "Add new Curation" button (Figure 3, orange arrow) located on your Dashboard (Figure 3, orange box).

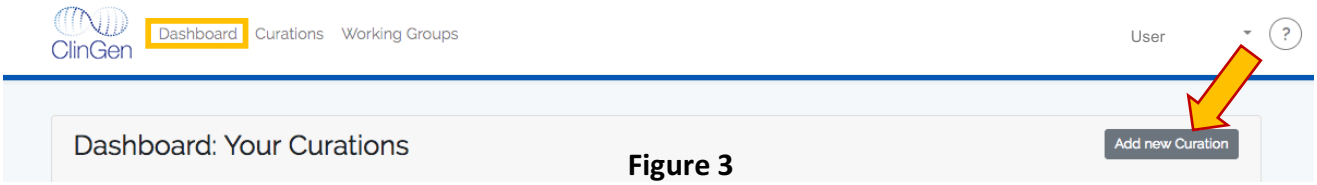



**Figure 3**

2. From the resulting page (Figure 4) you will be prompted to enter an HGNC gene symbol, Gene Curation Expert Panel, curator, and notes. ***Only the HGNC gene symbol and Gene Curation Expert panel are required for entry.***

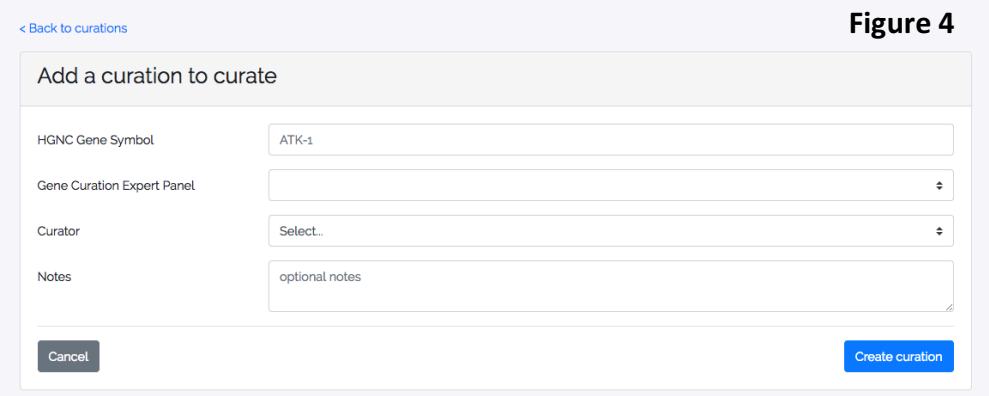



**Figure 4**

## 2. Selecting a curator

a. To designate a curator responsible for the gene precuration in your affiliation(s), use the drop down menu under the "Curator" heading (third line, Figure 5 orange arrow).
   i. If you find that the list of approved curators for your affiliation is not up-to-date, please contact the Gene Tracking System help desk at clingentrackerhelp@unc.edu.

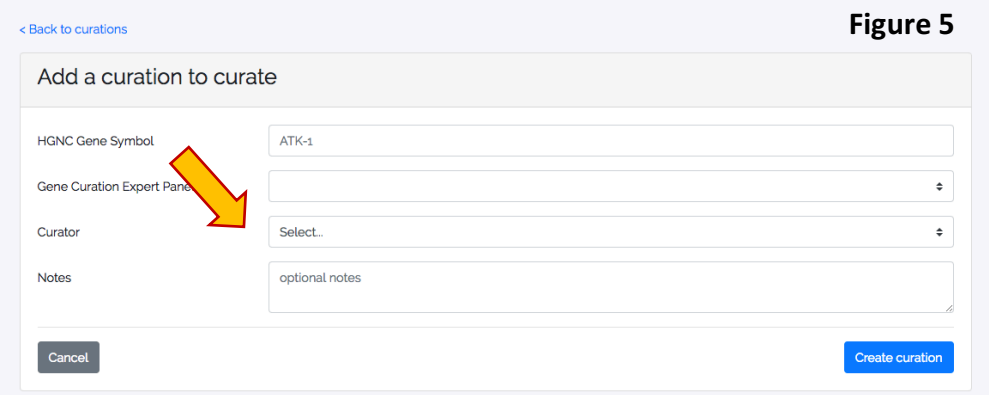


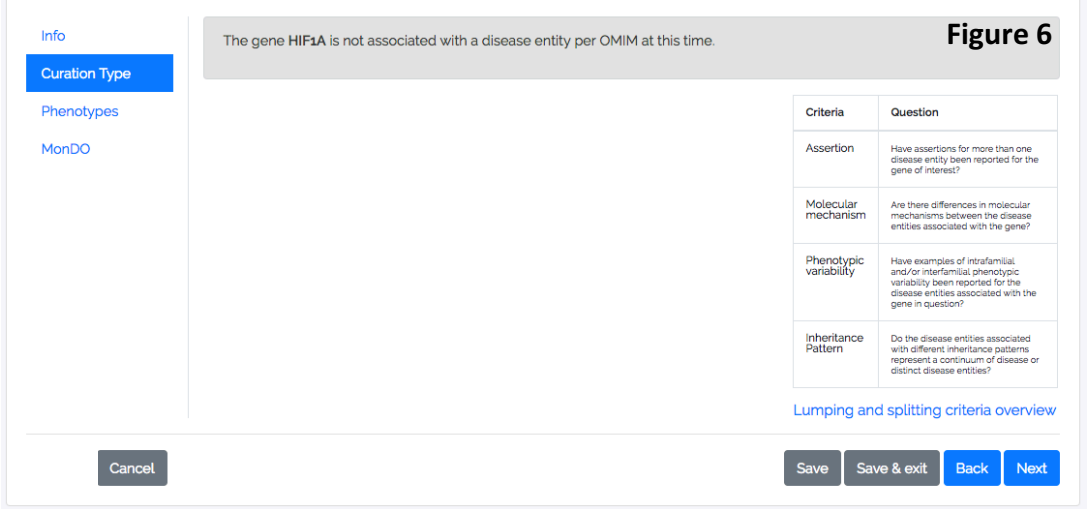

**Figure 5**

# For All Users:

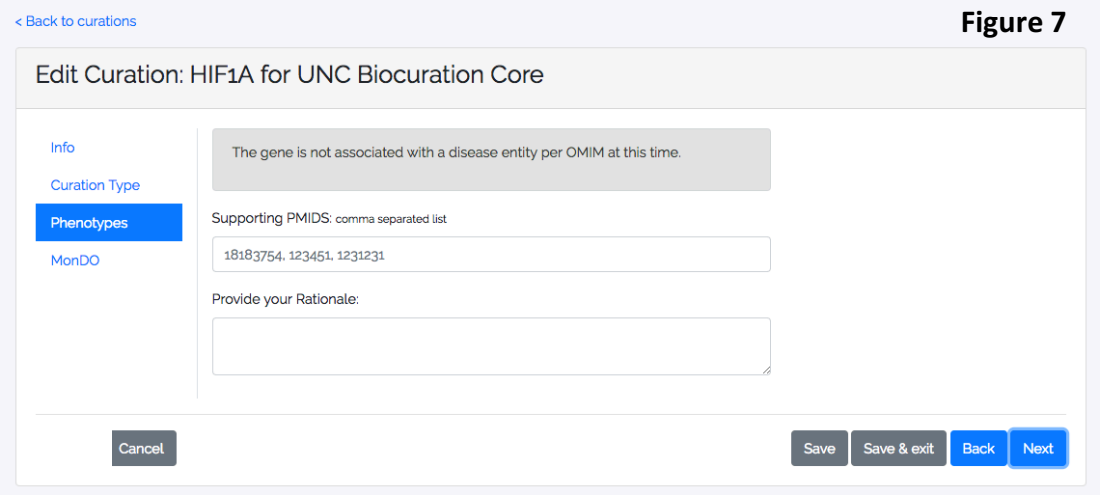
## 3. Precuration

The precuration process assists groups in determining the most appropriate disease entity(ies) to curate any given gene, and is outlined in the ClinGen Lumping and Splitting guidelines. After entering the name of the gene (HGNC) and curation expert panel, you will be directed to one of three options depending on how the gene is associated with disease per OMIM:
(a) the gene is **not** associated with a disease entity per OMIM,
(b) the gene is associated with a single disease entity per OMIM,
(c) the gene is associated with multiple disease entities per OMIM.

a. For genes **not** associated with a disease entity in OMIM, the Gene Tracking System will give this information on the "Curation type" tab (Figure 6). The Lumping and Splitting Criteria are provided, as well as a hyperlink (Lumping and Splitting criteria overview). **Click Next.**




i. On the "Phenotypes" tab of the curation entry, the user is prompted to provide evidence supporting that the gene is involved in the disease entity planned for curation, including any relevant PMIDs and/or textual rationale (Figure 7).
ii. Addition of either supporting PMIDs or rationale is required to proceed.




iii. On the "MonDO" tab of the curation entry, the user is prompted to provide a MONDO ID for the disease entity associated with the gene curation.
    1. A link to MONDO Ontology Lookup Service (OLS) is provided below the MONDO ID entry, underlined in blue (Figure 8, orange arrow).

2. In the event that there is not an appropriate MONDO ID, use the Disease Entity box to provide the preferred disease nomenclature based on expert guidance.

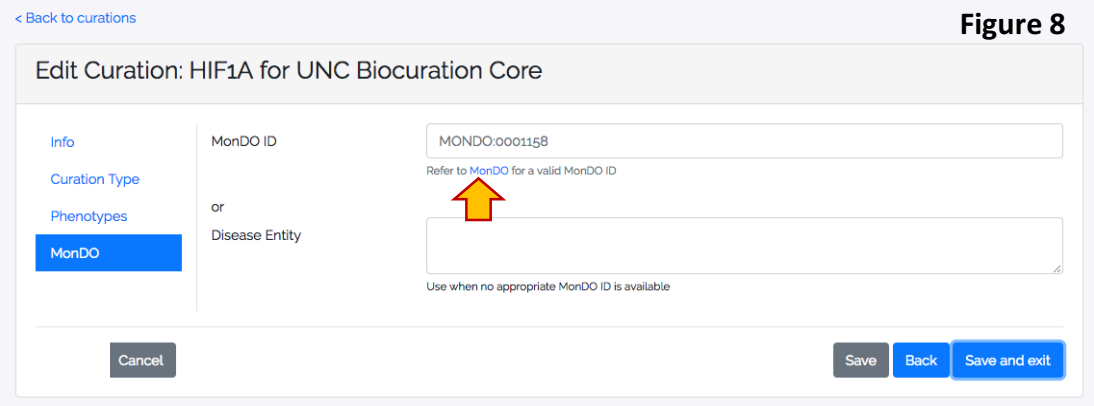



**Figure 8**

3. **Please contact the Lumping and Splitting Working Group (courtney_thaxton@med.unc.edu) for directions on how to acquire an appropriate MONDO ID.**
4. Push "Save and exit" for completion of this record.

b. For genes associated with a single disease entity per OMIM, the Gene Tracking system will return the disease entity on the "Curation Type" tab (Figure 9).

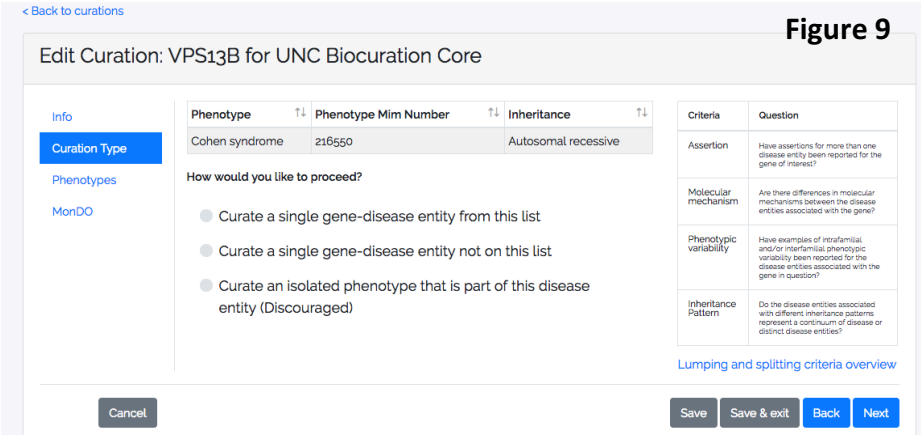
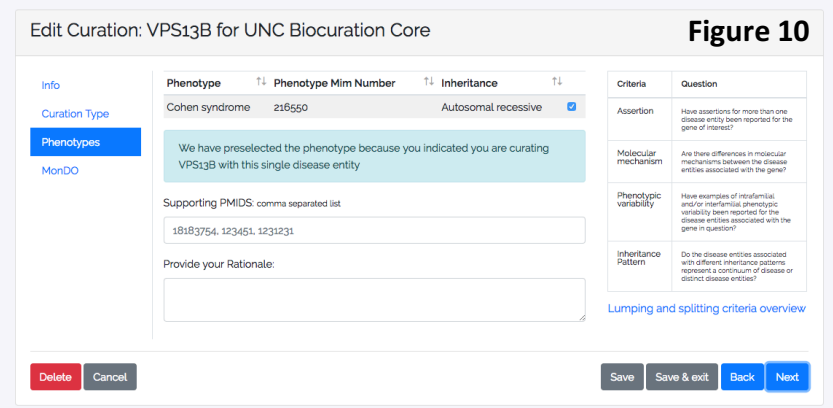



**Figure 9**

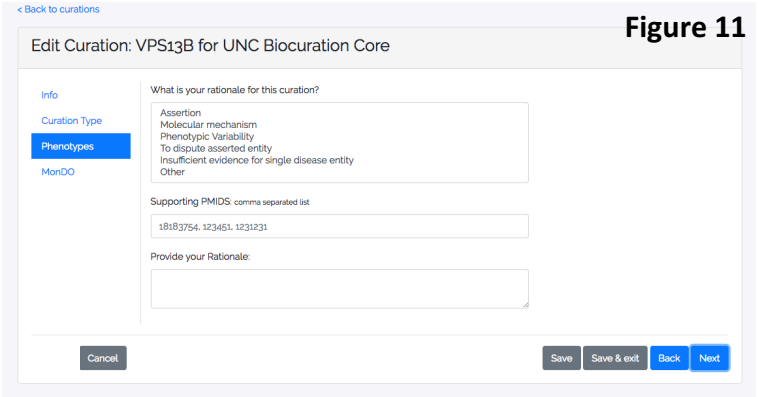
i. The user is then prompted with one of three choices:
   1. Curate the single disease entity on this list (encouraged)
   2. Curate a single disease entity not on this list (to indicate a new gene-disease association).
   3. Curate an isolated phenotype that is part of this disease entity (discouraged).
      a. This availability of this choice recognizes that some groups may want to curate a specific phenotype that is part of a greater syndrome, but which would not qualify as a separate disease entity based on the Lumping and Splitting Guidelines.

ii. When choosing "Curate the single disease entity on this list," the Gene Tracking System will advance to the "Phenotypes" tab of the curation entry and ask for the user to provide supporting evidence, including PMIDs and/or textual rationale (Figure 10).

1. Once the supporting evidence is provided, the user will progress to the MonDO tab and will be asked to provide a MONDO ID or disease entity (***as in Figure 8***).

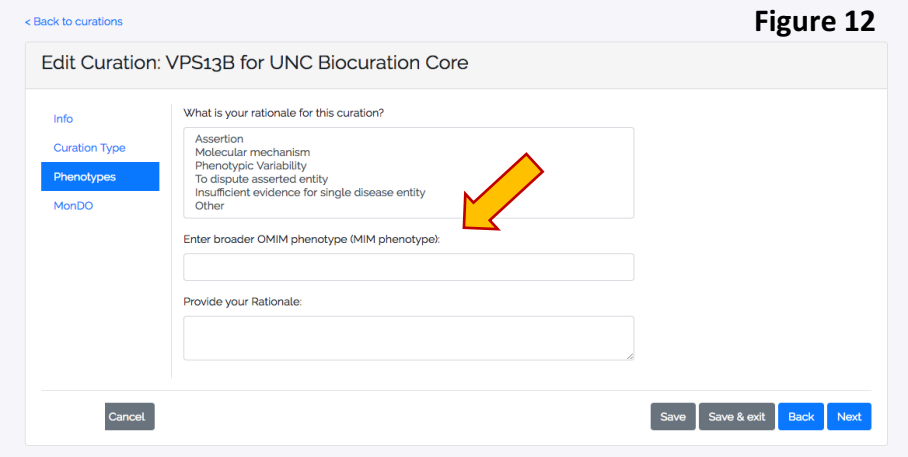



iii. When choosing "curate a single disease entity **not** on the list" the Gene Tracking System will prompt the user to provide supporting evidence concordant with the Lumping and Splitting guidelines on the "Phenotype Tab" (Figure 11).
    1. On the drop down menu, the user can choose one or more of the rationales consistent with the Lumping and Splitting criteria.
        a. For multiple selections, hold down the command (or windows) key and select the criteria.
    2. Either rationale or PMIDs are required to progress.
    3. Once the supporting evidence is provided, the user will progress to the MonDO tab and be prompted to provide a MONDO ID or disease entity nomenclature (***as in Figure 8***).



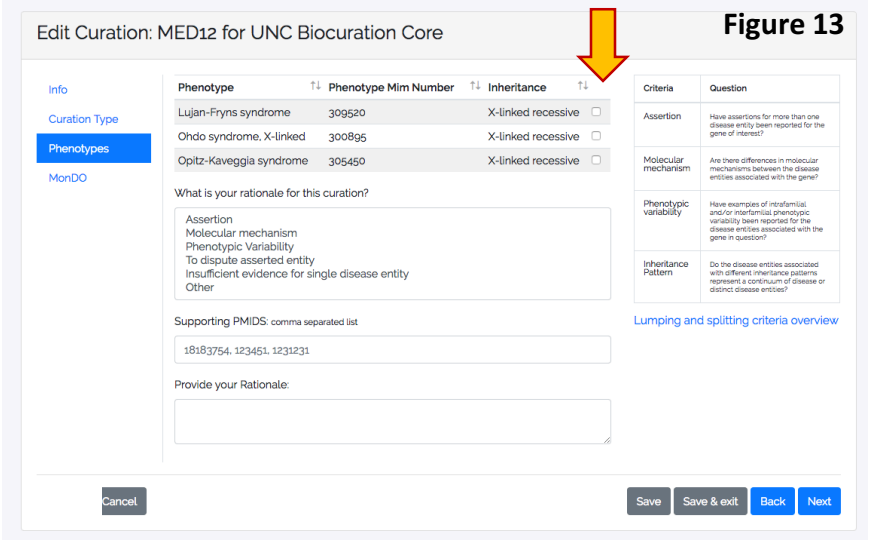

iv. When choosing "curate an isolated phenotype that is part of this disease entity" the Gene Tracking System will progress to the "Phenotype" tab and ask the user to provide supporting evidence.
    1. The user is prompted to enter the broader OMIM phenotype (MIM Phenotype number) if the entity they have chosen to curate is a single phenotype (Figure 12 orange arrow).
    2. Once the supporting evidence is provided, the user will progress to the MonDO tab and be prompted to provide a MONDO ID or disease entity nomenclature (***as in Figure 8***).
        a. As these curations are phenotypic driven, use of the free text box to define the phenotype is recommended, instead of a MONDO ID.

**Figure 12**




c. For genes associated with multiple disease entities per OMIM, the Gene Tracking System will return the disease entities (phenotypes per OMIM) on the “Curation Type” tab.
    i. The user is prompted with the following choices for curation:
        1. Curate a single gene-disease entity from the list (see Section 3bii-1 for data entry instructions).
        2. Curate a single gene-disease entity not on this list (see Section 3biii-1-3 for data entry instructions).
        3. Curate an isolated phenotype that is part of this disease entity (Discouraged) (see Section 3biv-1 for data entry instructions).
        4. Curate a “lumped” disease entity from this list.
    ii. When choosing to curate a “lumped” disease entity from the list on the “Curation Type” tab, the Gene Tracking System will progress to the “Phenotypes” tab.
        1. On the “Phenotypes” tab check the disease entities that will be part of the lumped disease entity, by clicking the associated OMIM phenotypes on the far right of the inheritance (Figure 13, orange arrow). Also provide the required rationale.

**Figure 13**




        a. Once the supporting evidence is provided, the user will progress to the MonDO tab and be prompted to provide a MONDO ID or disease entity nomenclature (***as in Figure 8***).

# 4. Searching and viewing gene information

a. To view the entire gene list, navigate to the 'Curation' tab at the top of the page (Figure 14, orange box).


**Figure 14**

b. To search for genes on the entire list by the Expert Panel, Curator, Status or Disease entity (MONDO ID), use the search bar (Figure 15, orange arrow) in the 'Curations" tab.
   i. To search by gene in your specific affiliations, use search bar within the 'Dashboard' tab.

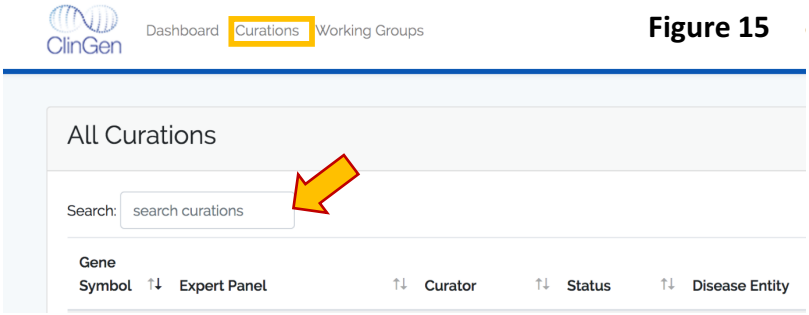



**Figure 15**

c. To view the information captured for a specific gene precuration, use either the search box (directions from 4bi above) to enter the HGNC nomenclature of the specific gene, or scroll through the list, then click on the gene symbol (Figure 16, orange arrow).

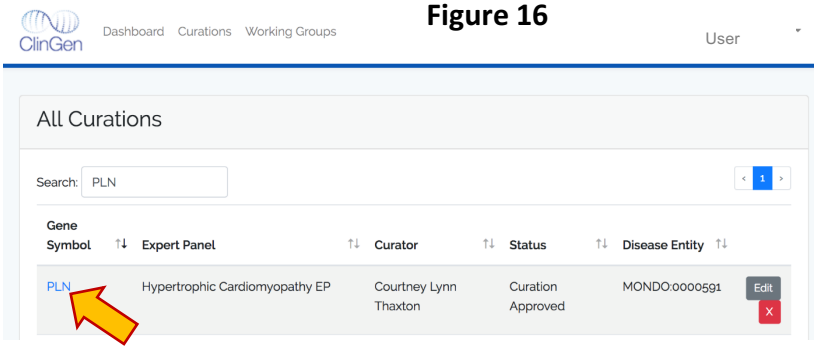
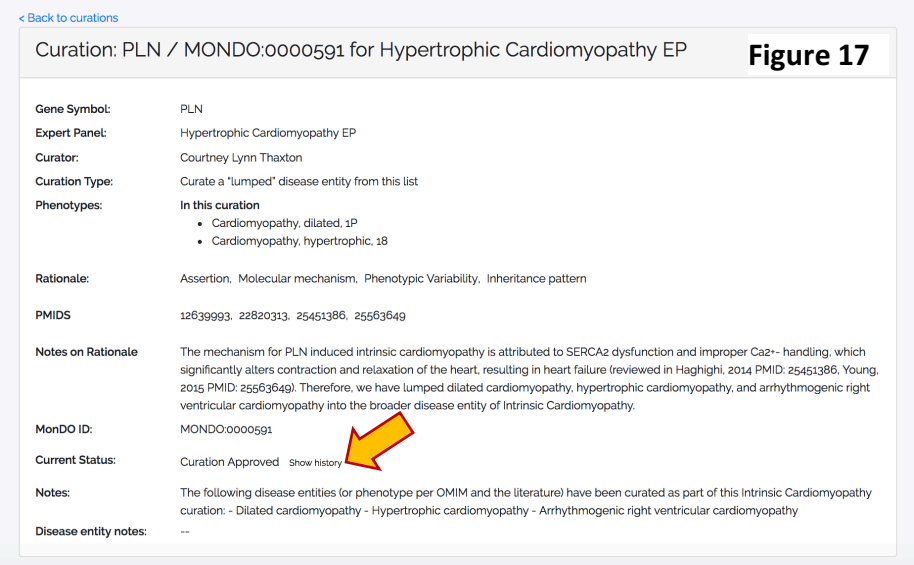


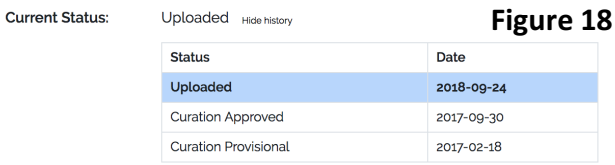

**Figure 16**

   i. Once the gene symbol is clicked, the resulting page will list all available precuration information gathered by the specific Expert Panel (Figure 17).

1. Evidence presented can include the gene symbol, Expert Panel performing the precuration, curator, curation type, phenotypes (or disease entities) included in the curation (important in lumped disease entities), rationale, PMIDs supporting the disease entity, MonDO ID, and curation status.

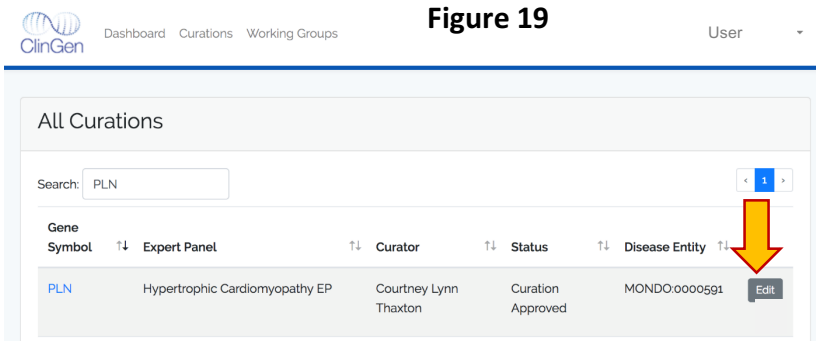



2. To view status history, click the 'Show history' tab on the gene curation information page (Figure 17, orange arrow). It will expand a table that outlines each entered status and the date (Figure 18).




# 5. Editing precuration information

a. Editing gene precuration is restricted by affiliation and role designation. Coordinators can edit all gene information for their specified affiliations. Curators can only edit gene information for those genes to which they were assigned the precuration, unless granted editing capabilities (See Permissions review above).
   i. To edit precuration information, go to your 'Dashboard' (Figure 3, orange box), and select the gene of interest (use search box to quickly recall the gene of interest) and select the 'Edit' button (Figure 19, orange arrow).



ii. After selecting the 'Edit' button, the gene 'Info' page will open. This allows for editing of the HGNC gene symbol, Curation Expert Panel, curator, notes, and status (Figure 20). **Be sure to click either the 'Save' or "Save and Exit' button before closing the page.**

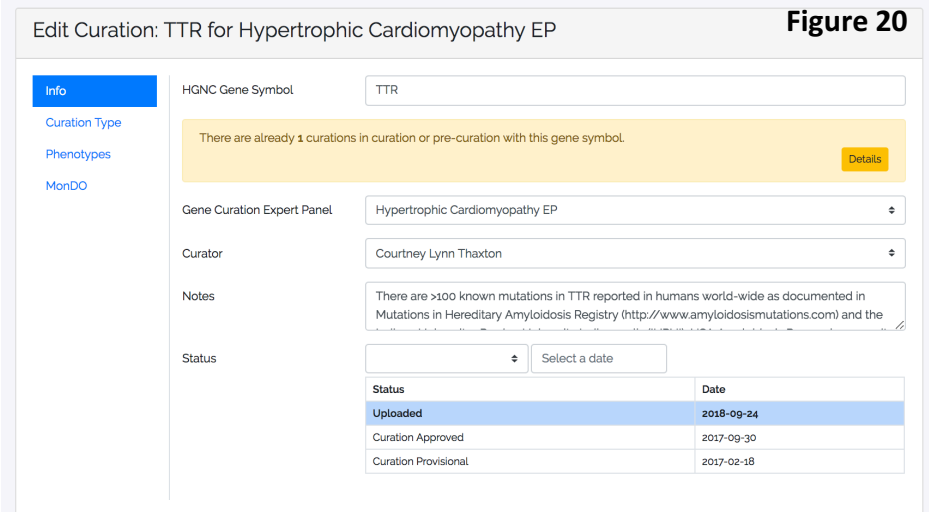



**Figure 20**

b. ***If a Coordinator needs to delete a gene precuration record, please contact the ClinGen Gene Tracking System helpdesk at*** clingentrackerhelp@unc.edu.

# 6. Notification of gene precuration multiplicity

a. For some genes associated with multiple disease entities, more than one curation will be appropriate, whereas one broader lumped disease entity may be the most appropriate for others. In order to alert users of any overlap, the Gene Tracking System has internal flags to notify the user if a gene of interest has been precurated by another Expert Panel.

i. Use the search box on your 'Dashboard' page, or the 'Curations' page to look up a gene of interest by name. The search function will return the current information for the gene of interest (Figure 21).

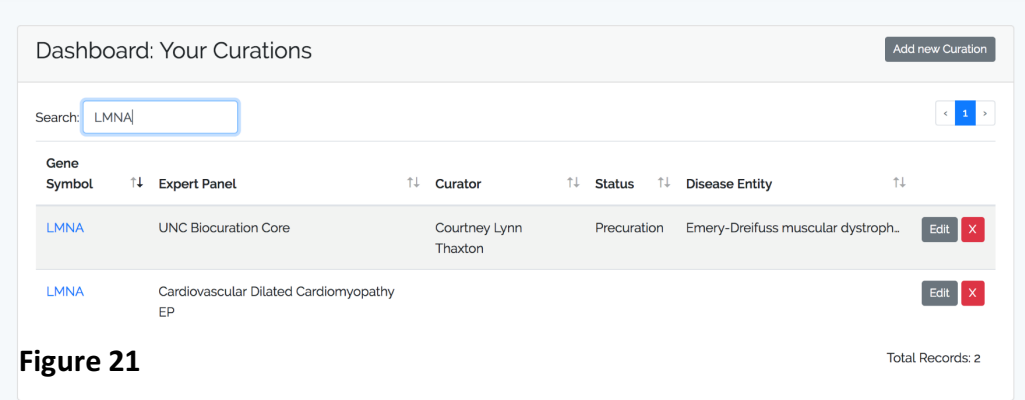



**Figure 21**

ii. When using the "Add new Curation' button to manually enter a gene for precuration (Steps 1aii-1, Figure 3), a user is alerted to duplicate/multiple gene entries by the appearance of a yellow box (Figure 22).

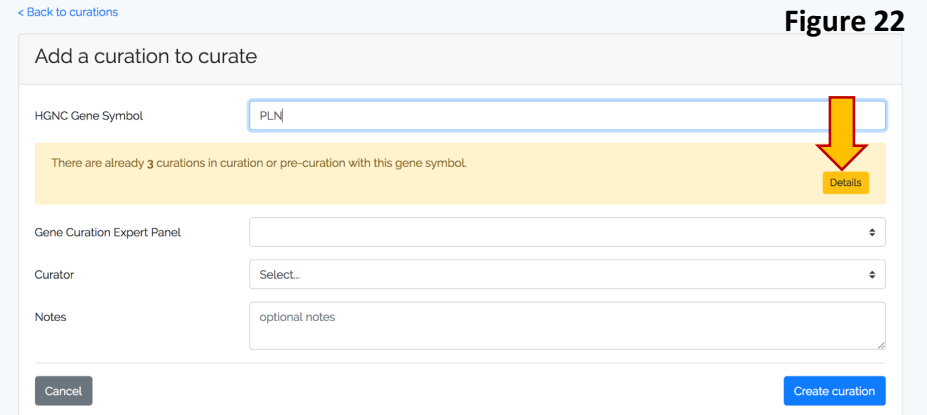



**Figure 22**

iii. Select the 'Details' button in the yellow box (Figure 22, orange arrow) to view the following details: The Expert Panels that are interested in the gene, the status of the gene curation, and the phenotypes/disease entities that were included in the curation, if applicable (Figure 23).

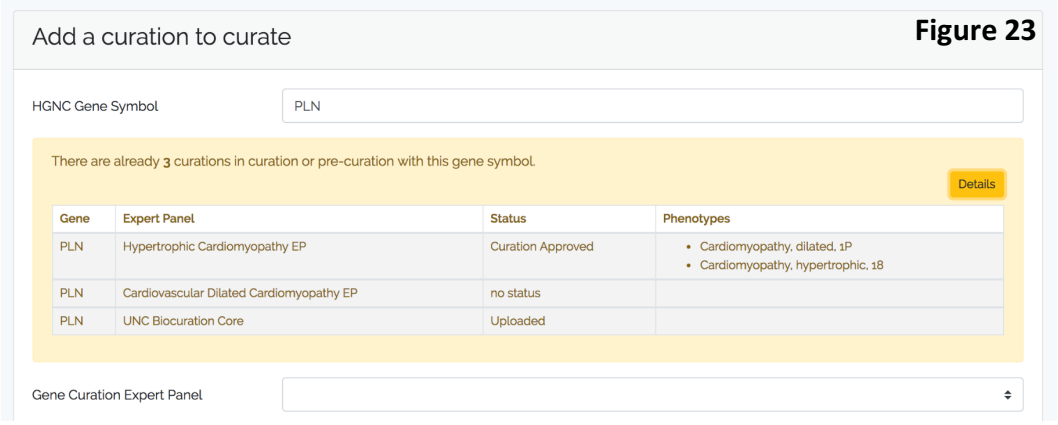



**Figure 23**

iv. In addition, the user will be alerted to duplicity/multiplicity of the gene curation on the 'Phenotypes' tab of the precuration process (see Section 3ai for one reference to this tab) by a yellow box (Figure 24).

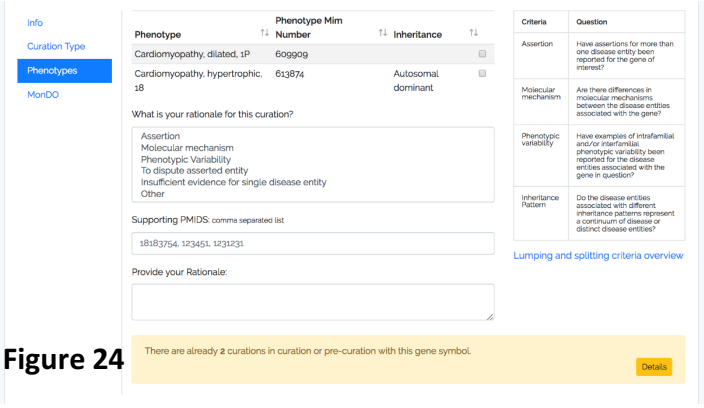


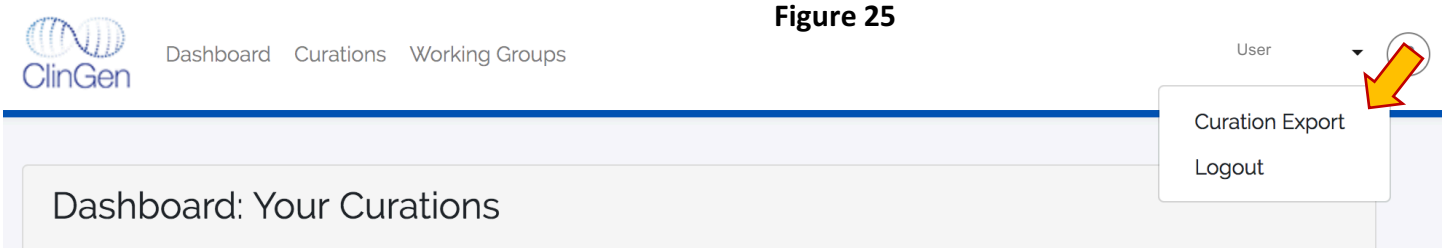

**Figure 24**

v. ***Note, entry of genes is not restricted and there may be multiple entries for the same gene-disease pair. In that case, it is strongly recommended to talk with other affiliations who have curated/are curating the same gene or gene-disease pair to avoid duplication of effort and to collaborate on the curation if needed (see "Working Groups" tab to find contact information, Section 8 below). Please note, only one record per gene-disease pair is allowed in the GCI. If an Expert Panel finds that a disease entity must be split for curation they can provide the supporting evidence accordingly. However, if a user or EP finds that a curation has already been performed by another group, and needs to delete their entry, they may contact the administrators at*** clingentrackerhelp@unc.edu.

# 7. Exporting Curation Data

a. To assist in tracking of curation efforts, milestones, and progress, a "Curation Export" function is available for use.
   i. Click the arrow to engage the dropdown menu under your user name, and select the "Curation Export" option (Figure 25, orange arrow).

**Figure 25**




   ii. From the curation export page, one can choose to download gene curation information (in an Excel file) from either a specific Expert Panel, or "All" efforts can be chosen (Figure 26, orange arrow).
      1. A date range can be selected for the download. **Note, if no date range is chosen, the entire gene list will be downloaded.**

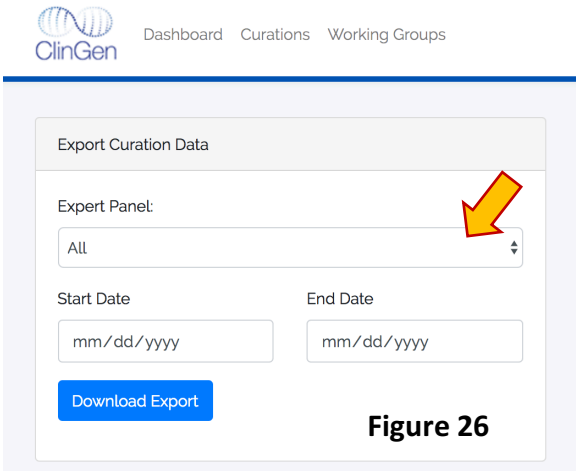



**Figure 26**

# 8. Working Groups Tab

b. The “Working Groups” tab on the Gene Tracking System provides important information on the curation efforts, including: (1) the Expert Panel Affiliations associated with each ClinGen Clincal Domain “Working Group;”(2) the name, email, and role for each Expert Panel member; and (3) the list of gene-disease curations for each Expert Panel.

i. Choose the “Working Groups” Tab from the top, left menu bar (Figure 27, orange box).


**Figure 27**

ii. Next choose the specific Clinical Domain “Working Group” of interest (Figure 28).

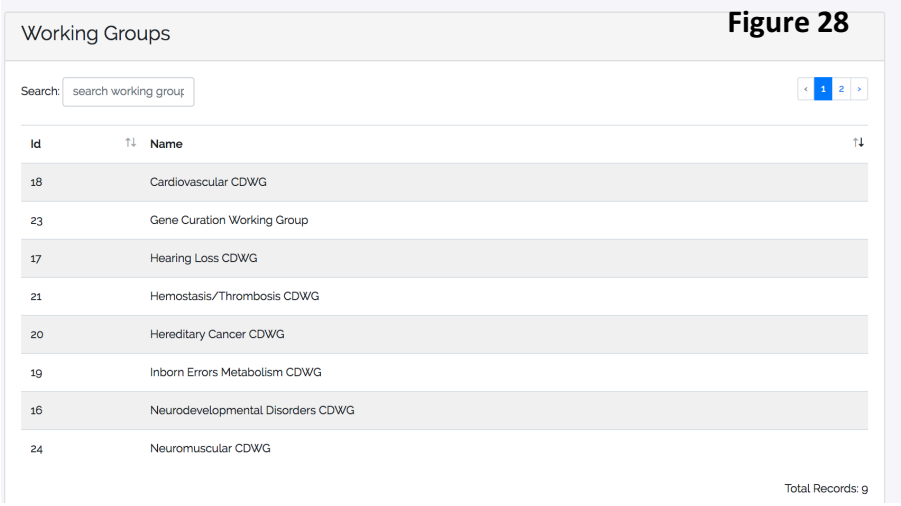



**Figure 28**

iii. One can then choose the specific “Expert Panel” for display of the membership. The “People” tab is the default initial information displayed (Figure 29, orange arrow).

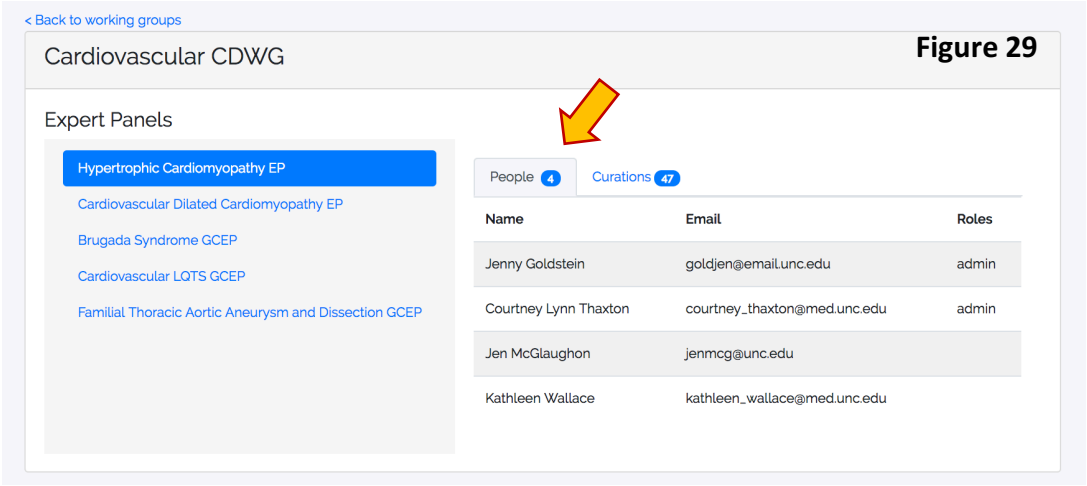



**Figure 29**

iv. To review the curation efforts for a specific Expert Panel, make sure the expert panel is highlighted in dark blue (e.g. UNC Biocuration Core, Figure 30), and then choose the “Curations” tab (see Figure 30, orange arrow).

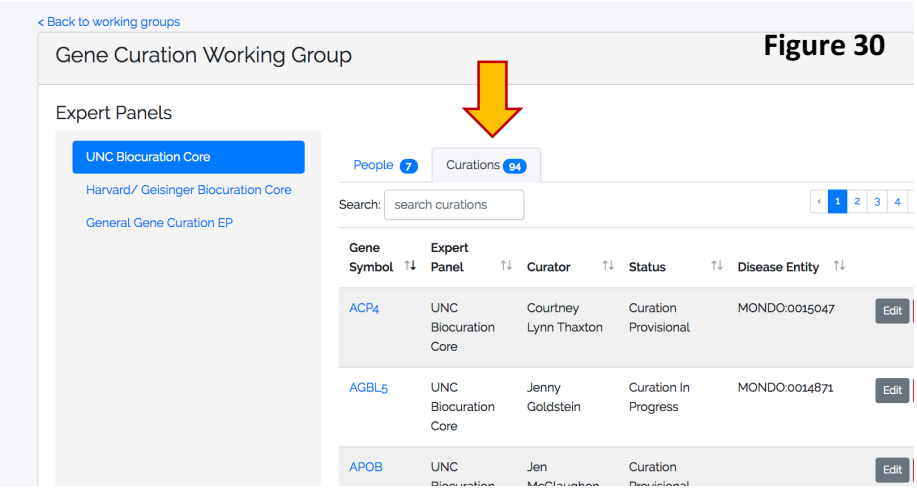



**Figure 30**