Variant Curation Interface

Help Documentation

August 2016 Test Release

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Feedback / Comments?

Please email us at: clingen-helpdesk@lists.stanford.edu

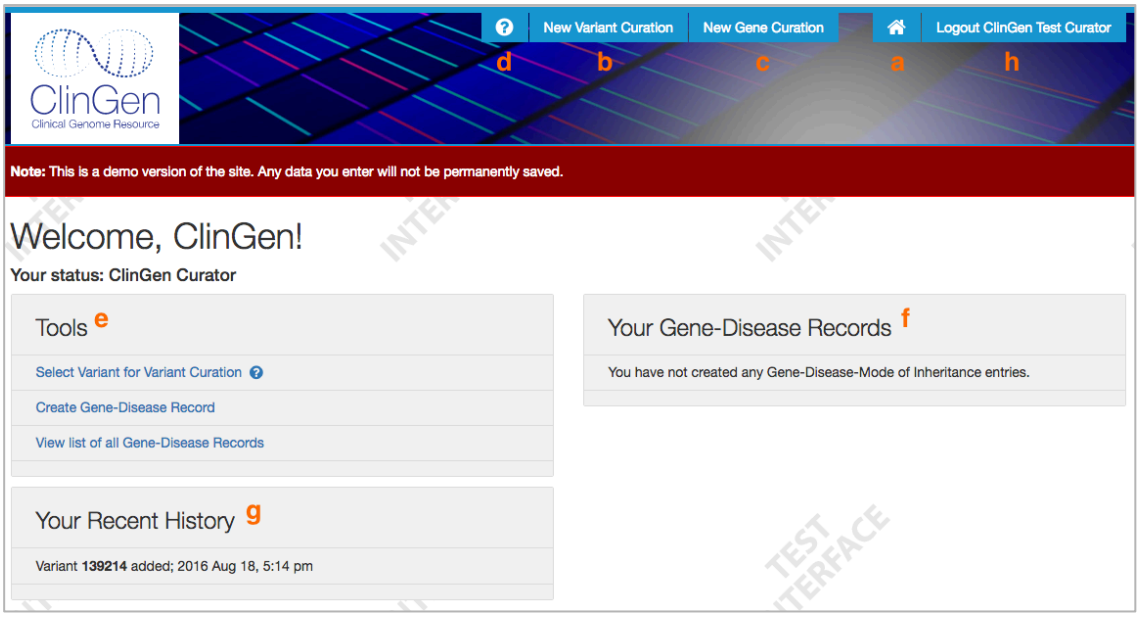
GENERAL NAVIGATION

1. Logging in to the interfaces

Go to https://variant-curation-alpha2.demo.clinicalgenome.org/ and click the “Login” button. If you are registered but have not yet created a Persona account, you will be prompted to do so.

2. Dashboard view

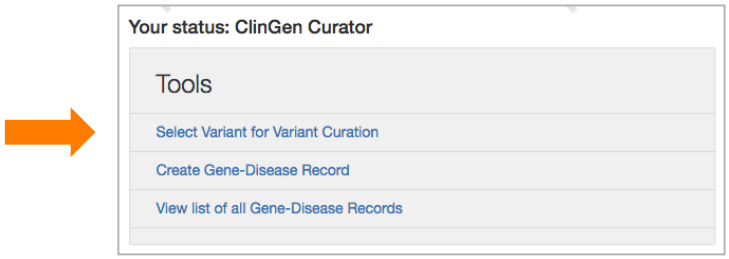
a. Dashboard home – available from all pages
b. Navigating to “Select Variant for Variant Curation” – available from all pages
c. Navigating to “Create Gene-Disease Record” – available from all pages
d. Navigating to this Help documentation online – available from all pages
e. Tools – useful links
f. View of your current gene-disease curation records *(variant curation records will appear in next release)*
g. View of your recent history
h. Logout – available from all pages



SELECTING A VARIANT FOR VARIANT CURATION

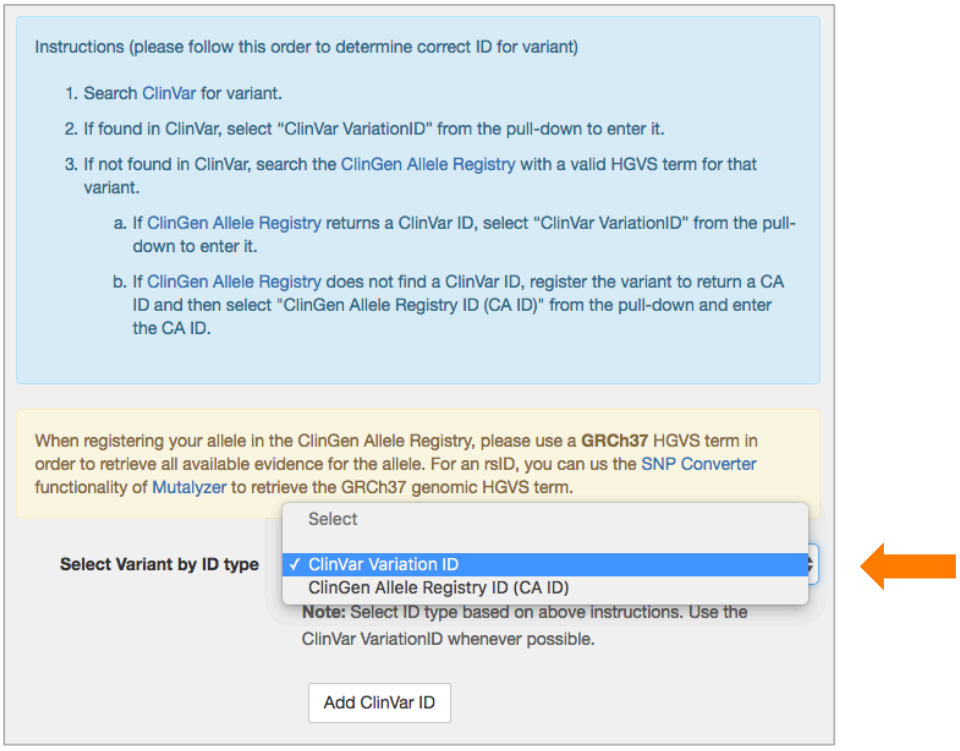
1. Begin variant curation

Select “Select Variant for Variant Curation” under the “Tools” Section



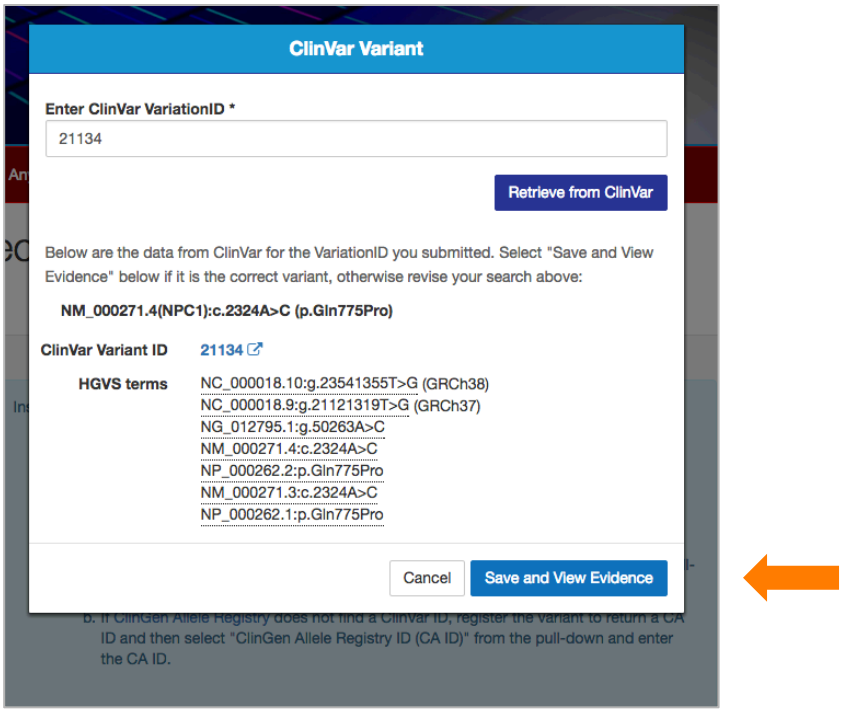
2. Select variant ID

Read instructions carefully on how to select a variant, and then choose whether you want to enter a ClinVar variant using a ClinVar Variation ID or a novel variant that you have registered with Baylor’s ClinGen Allele Registry. Select “Add ClinVar ID.”



Type in the variant ID (ClinVar VariationID or CA ID, depending on selection); click “Retrieve from ClinVar” (or “Retrieve from ClinGen Allele Registry, if you have entered a

CA ID). Once you are convinced the ID you have entered represents the correct variant, select “Save and View Evidence.”

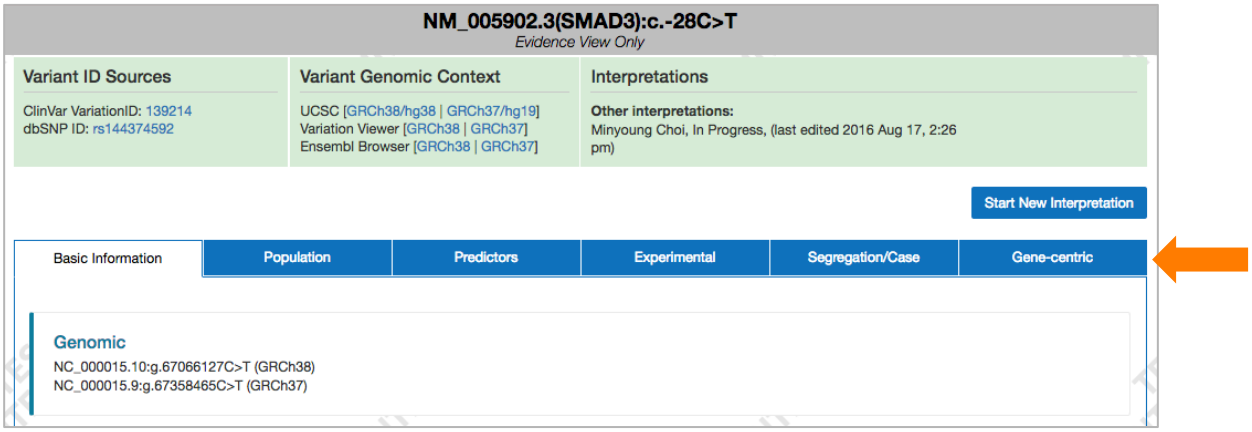


3. You will now be in the “Evidence View” for your selected variant.

GENERAL ORGANIZATION OF INFORMATION AND EVIDENCE

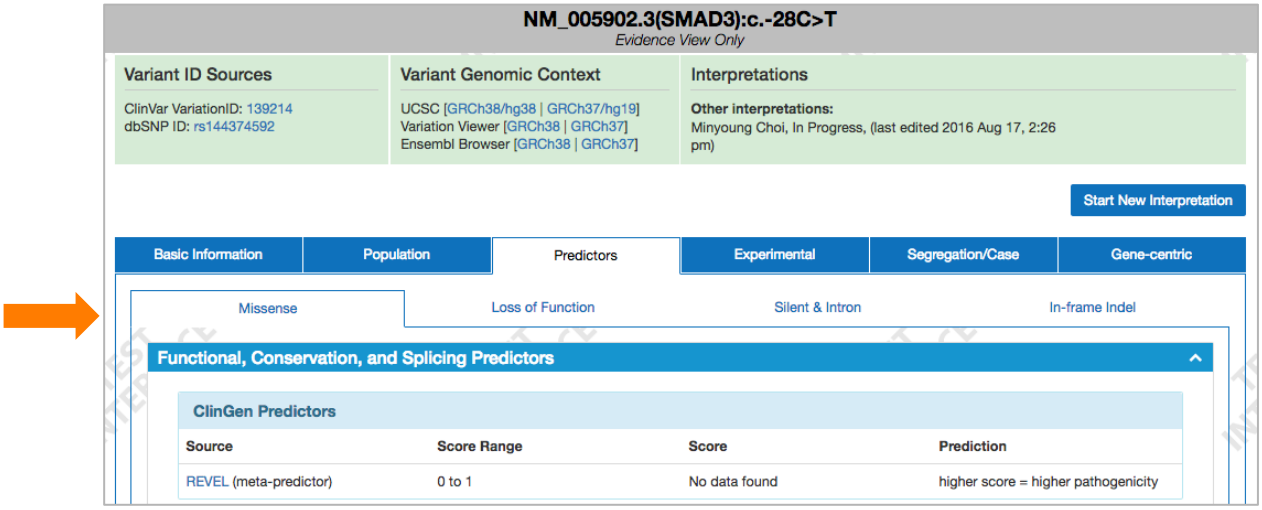
1. Overall tab organization

Once you are in the "Evidence View only," you will see the information and evidence for the selected variant is organized into various tabs. These include: **Basic Information**, **Population**, **Predictors**, **Experimental**, **Segregation/Case**, and **Gene-centric**. Click between the tabs to view different types of information and evidence.



2. Predictors tab: sub-tab organization by variant type

The Predictors tab contains sub-tabs such that you can look at the appropriate evidence and evaluate the appropriate criteria according the to the variant type (**Missense**, **Loss of Function**, **Silent & Intron**, and **In-frame indel**).



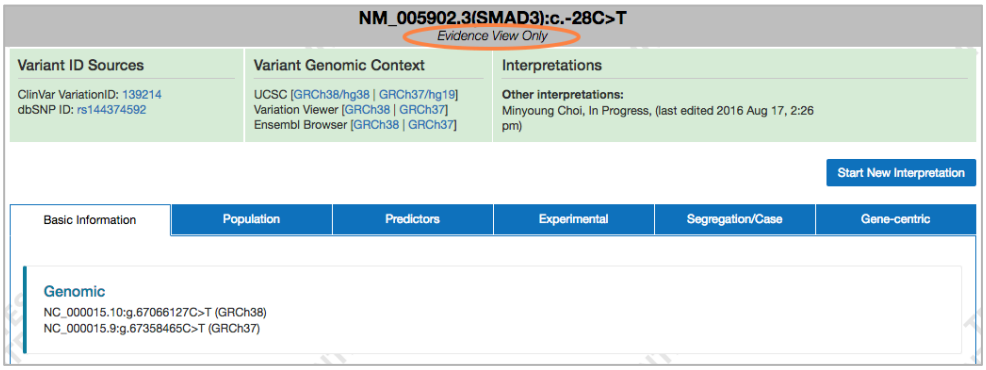
OVERALL WORKFLOW

Once you have selected a variant, there are currently 3 major modes:

1. Evidence View Only
2. Interpretation
3. Interpretation with Disease Association

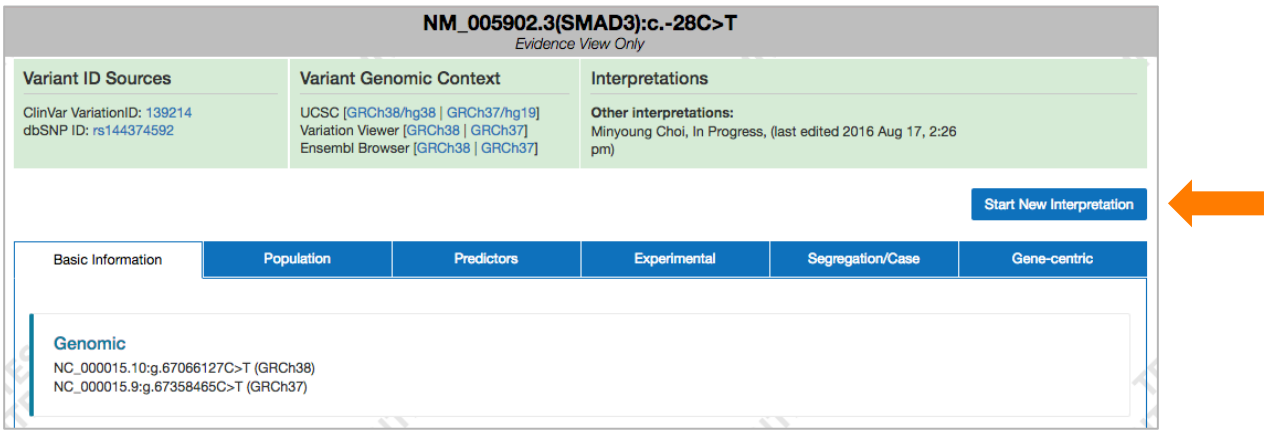
1. Evidence View Only

In this mode, you can view all the evidence associated with a variant, clicking between tabs. The ACMG criteria do not appear in this mode.



2. Interpretation Mode

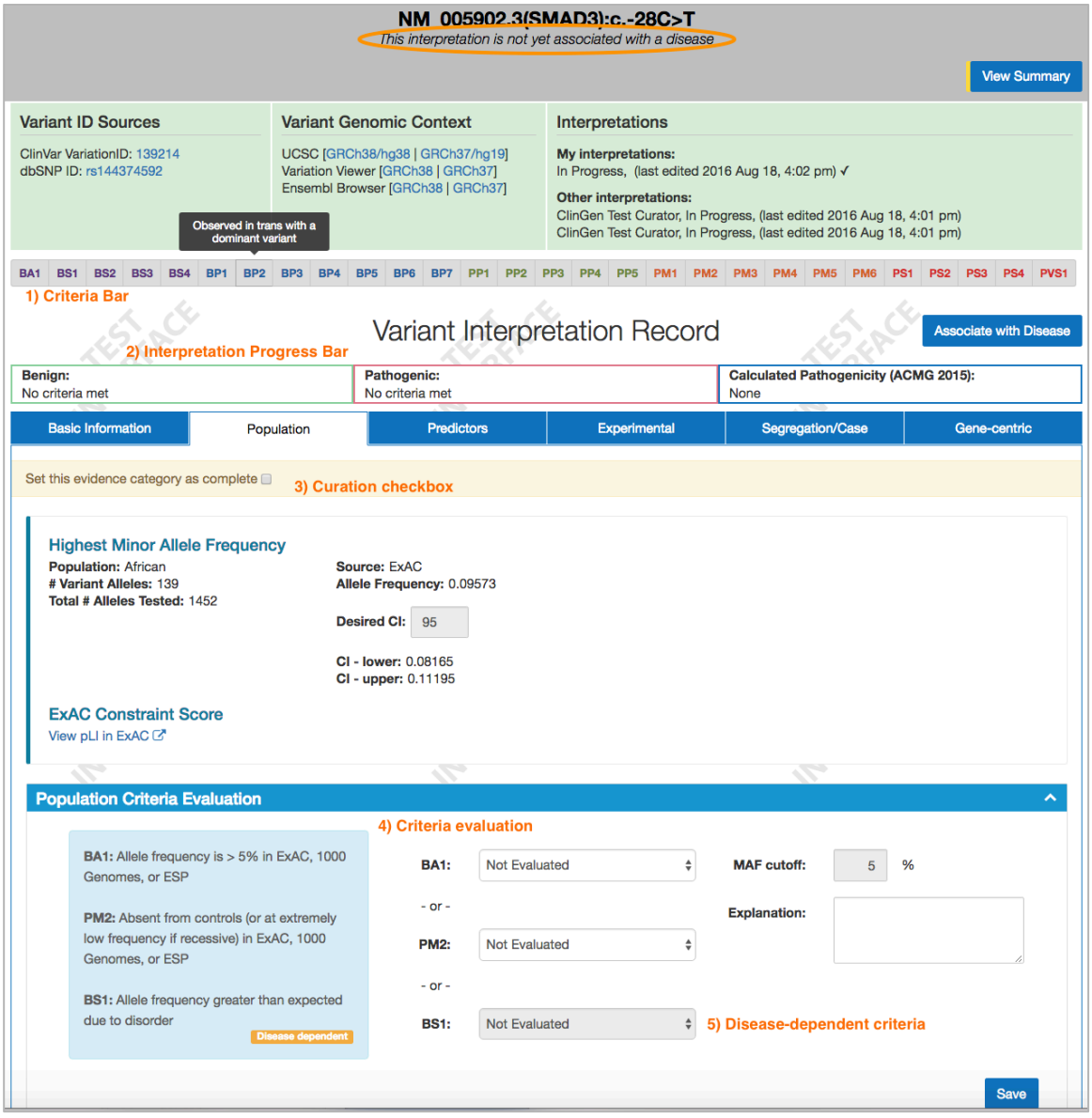
To begin an Interpretation in which you can evaluate the evidence according to the ACMG criteria, select “Start New Interpretation” (see arrow above). Note: if you have already begun and Interpretation for the variant and return, the button will instead say “Continue Interpretation.”



Once you click on “Start New Interpretation,” you will be in Interpretation mode.

Once in Interpretation mode, the following will appear:

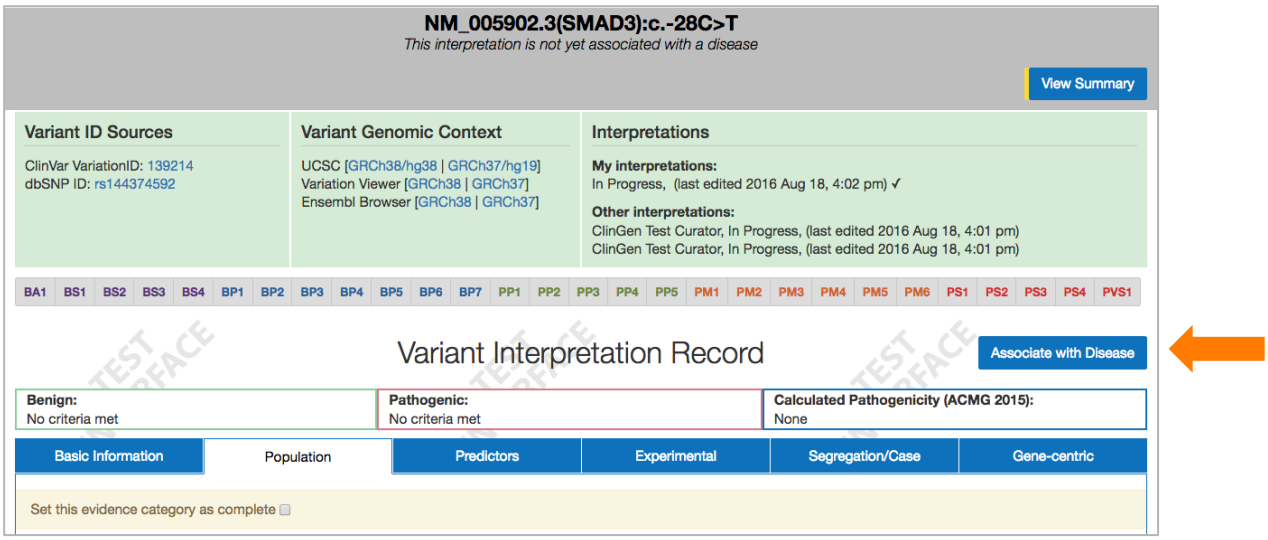
1) Criteria bar – scroll over a criteria to see the description of the criteria,
2) Interpretation Progress bar that indicates the strength of criteria met and the calculated pathogenicity
3) Checkbox on each tab that you can check when you have reviewed that category of evidence to your satisfaction
4) The criteria evaluations where you can indicate whether an individual criterion is "Met" *(see page 9 of this document)*
5) Disease-dependent criteria, which will be grayed out until a disease has been associated with the Interpretation (next step).



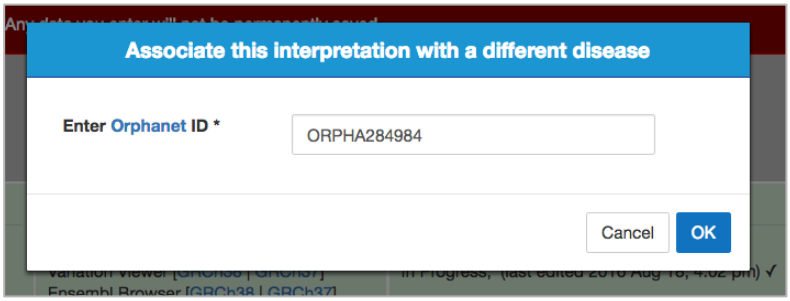
Note that the "View Summary" button in this version is not yet functional (indicated by the yellow bar to its left).

3. Interpretation with Disease Association

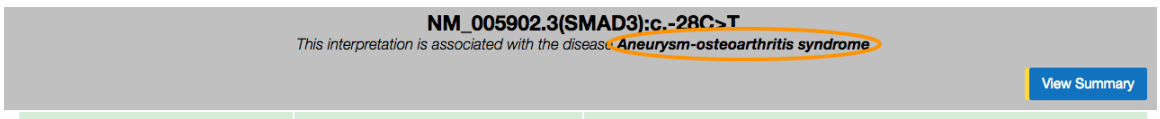
When you are ready to evaluate disease-dependent criteria for your Interpretation, you can click the “Associate a Disease” button to add the Orphanet ID for the disease. Be sure you’ve saved your evaluations before clicking this button.



After clicking the “Associate with Disease” button, you will see an entry box pop up for entering an Orphanet ID. Enter the desired Orphanet ID and click OK.



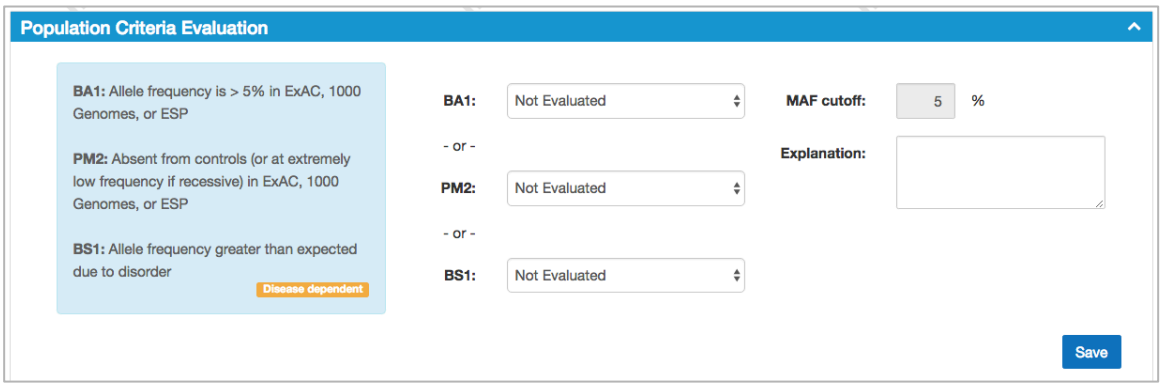
Now all disease-independent criteria evaluation boxes will become active and you will see the disease term under the variant name in the gray title area



EVALUATING CRITERIA

1. Criteria placement & organization

Criteria are grouped according to the evidence required for their evaluation and on the appropriate tab page.



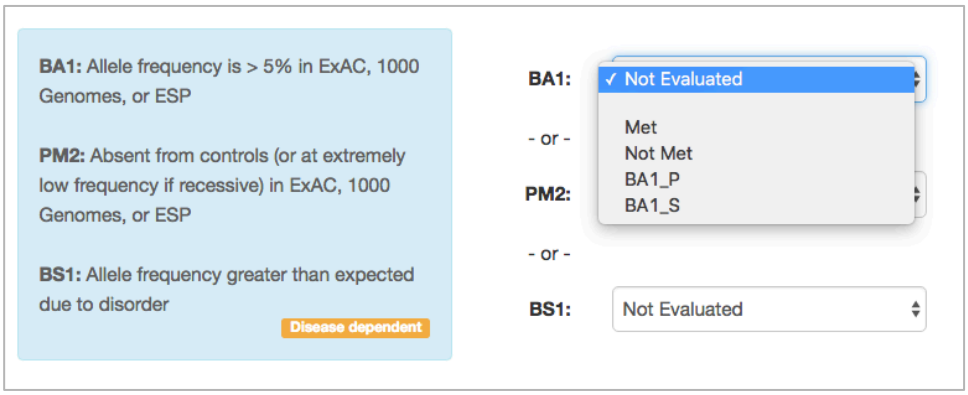
2. Criteria evaluation choices:

The pull-downs allow the following criteria evaluation choices:

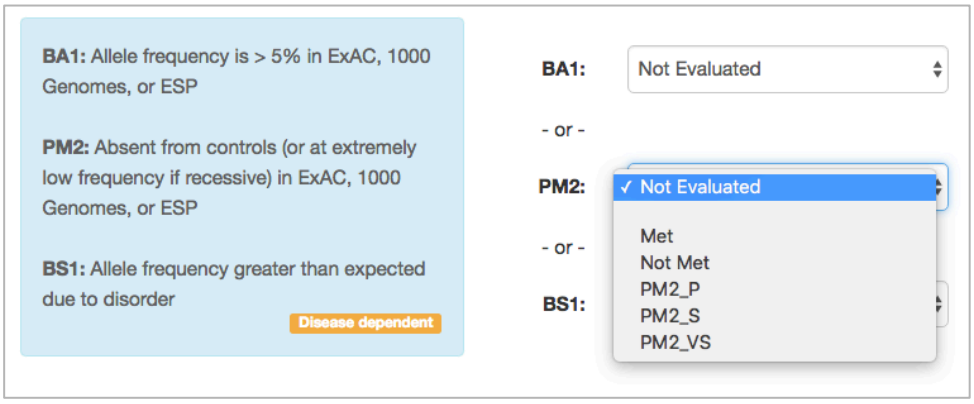
- **Not Evaluated**: The default state of an Evaluation is “Not Evaluated”
- **Met**: If the evidence supports a positive evaluation of a criterion at its original strength (e.g. PM2 = moderate strength in the pathogenic range), the curator should select “Met”
- **Not Met**: If the evidence does not support a positive evaluation of the criterion, the curators should select “Not Met.”
- **_S, _M, _P, _VS, _stand alone**: The strength of evaluation for a criterion can be adjusted by selecting one of the above representations of the criterion (e.g. PM2_P would be PM2 evaluated at the “supporting” (_P) level rather than its inherent level, moderate (M)). *Note: Benign criteria allow _P, _S, and _stand alone adjustments. Pathogenic criteria allow _P, _M, and _S adjustments (except for PS2, which also allows for PS2_VS).*

(See examples, next page)

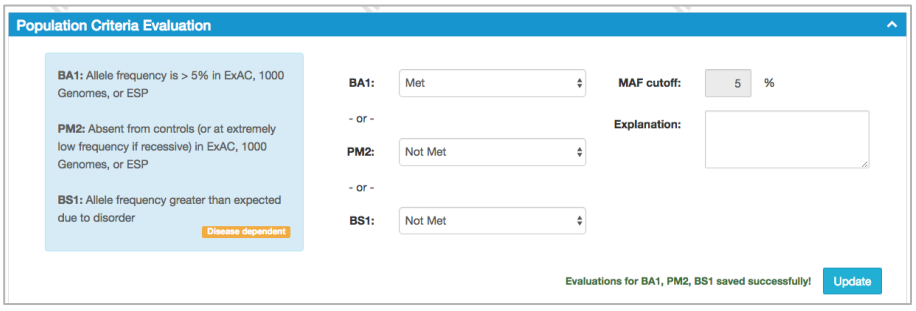
Benign pull-down choices – example:



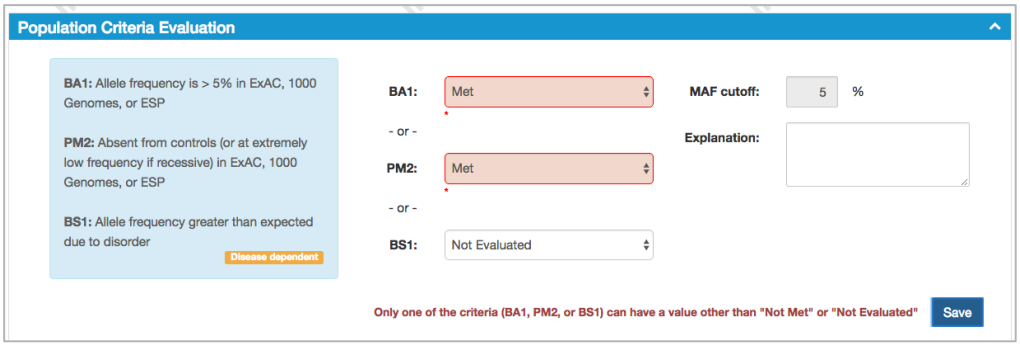
Pathogenic pull-down choices – example:



3. Steps for evaluating a criterion or criteria:
   - Examine evidence associated with criteria being evaluated
   - Select an evaluation for all criteria related to the evidence from the pull-down
   - Select Save
   - Note that the button will now change from “Save” to “Update” – if you would like to change an evaluation, change it and be sure to click “Update” after. The update button appears as a visual clue that the criterion/criteria for that section have already been evaluated.

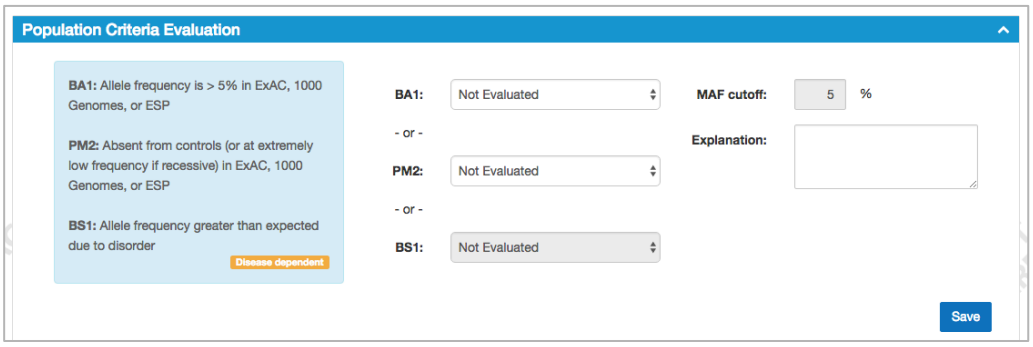


Note: When 2 (or more) criteria are opposites or cannot otherwise be "Met" at the same time, the interface will not allow "Met" to be selected for more than one of the criteria.

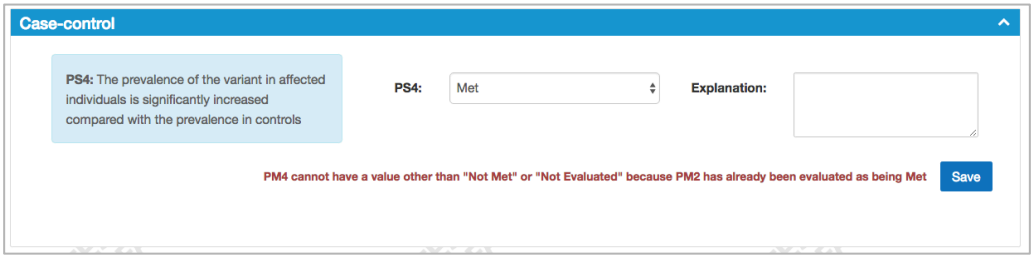


4. Additional notes:

If a criterion is grayed out, you will not be able to evaluate it until you associate a disease with the Interpretation (note BS1, below)



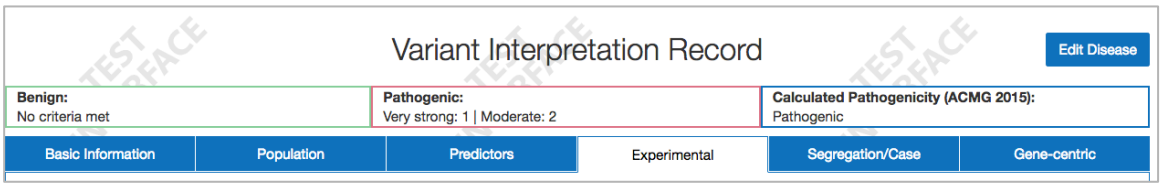
PS2 and PM4 may not both have positive evaluations – for instance, you will see this error if you select "Met" for PS2 (Population tab) and PM4 (Segregation/Case tab)



PATHOGENICITY CALCULATION

As you Save your evaluation, you will notice that the Progress bar will indicate the number of criteria met according to the strength of the evaluation and whether it is Benign or Pathogenic. Additionally, it will automatically calculate the Pathogenicity each time you Save or update an evaluation:

For instance, if PM2, PVS1 and PM1 are all met, the Progress bar would appear as follows immediately upon saving the last evaluation:

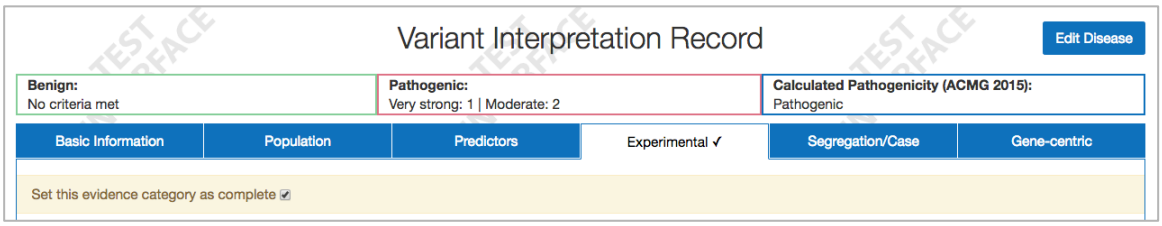


Pathogenicity outcomes:

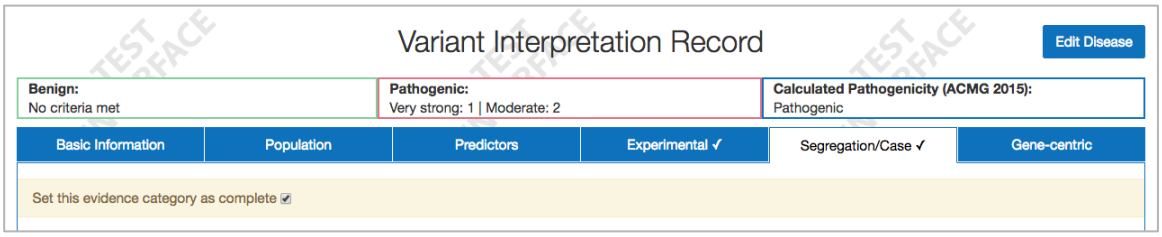
1. Benign
2. Likely benign
3. Pathogenic
4. Likely Pathogenic
5. Uncertain significance – insignificant evidence: there is not enough evidence to meet any of the above (1-4); there can be conflicting evidence
6. Uncertain significance – conflicting evidence: there is enough evidence to meet the above (1-4), but some of it is conflicting

CURATION CHECKBOXES ON TAB PAGES

If you have evaluated all the evidence on a particular tab page to your satisfaction, you can click the checkbox at the top of the tab page (for the Predictor tab, this means you have evaluated any relevant sub-tabs to your satisfaction) and a check will appear on the tab for your reference:



This checkbox will remain no matter which tab you are on in the interface and can be unchecked as well:



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