Panel of genes: design and analysis for clinical applications. TEAM

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GDA

International Course on

Genomic Data Analysis

PRINCIPE FELIPE

CENTRO DE INVESTIGACION

Introduction

- **Development of high throughput sequencing technologies**:
  - Fast and economical genome sequencing
  - Disease targeted sequencing: powerful and cost-effective application

- **Vast amount of biological knowledge available**:
  - HGMD-public, HUMSAVAR, ClinVar, COSMIC

- We need a tool to connect **sequencing data and biological knowledge for diagnostic:**
  - TEAM (**T**argeted **E**nrichment **A**nalysis and **M**anagement)

Introduction

Sequencing data

Biological knowledge

GWAS

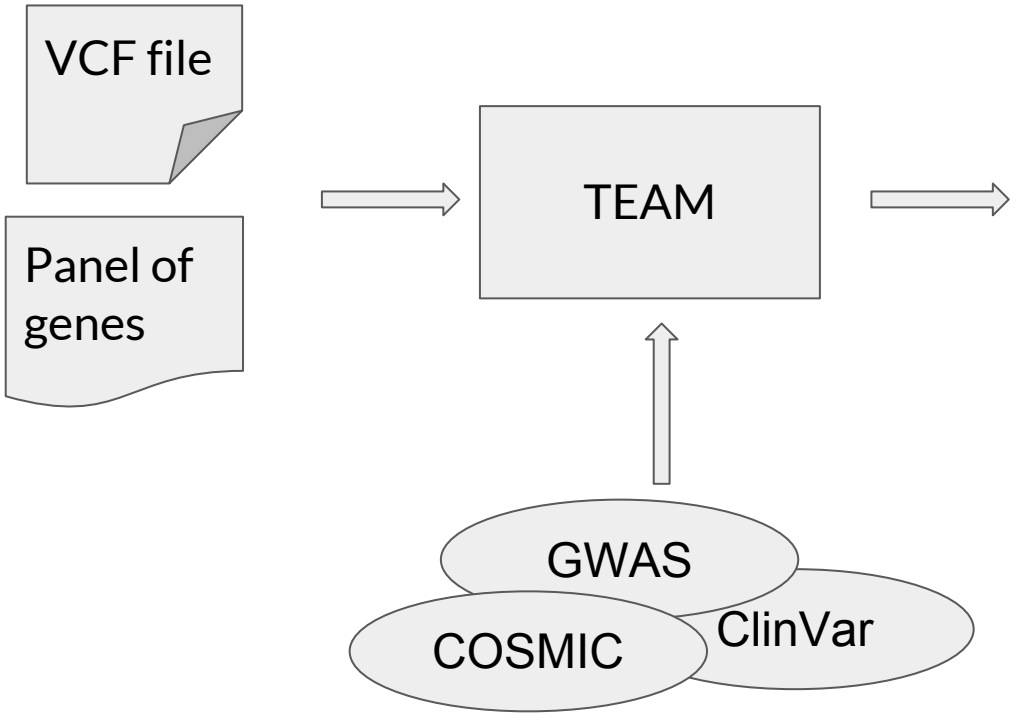
COSMIC

ClinVar

TEAM

Diagnostic

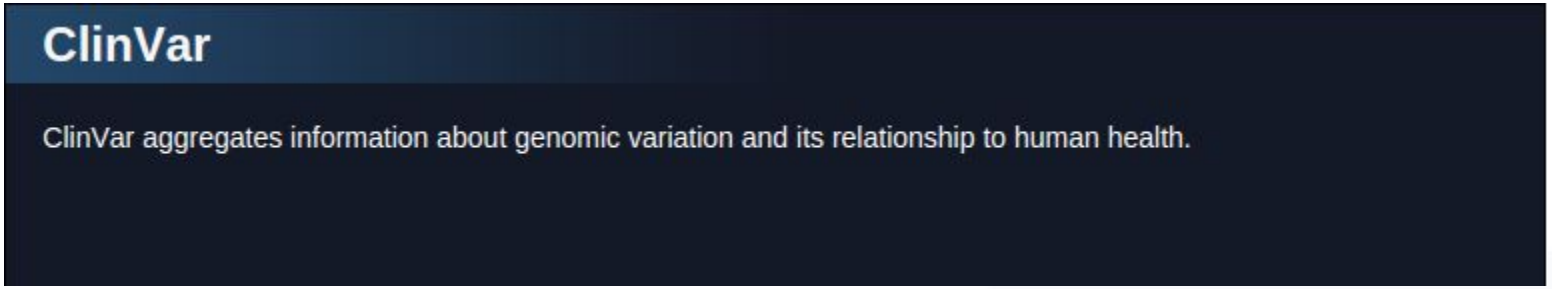
How does TEAM work?



Diagnostic

Chr	Pos	Ref	Alt	SNP Id
9	135786112	T	C	rs6597586
9	135786904	A	G	rs1073123
19	55453134	G	A	rs775886

Getting information



COSMIC
Catalogue of somatic mutations in cancer

GWAS Catalog

The NHGRI-EBI Catalog of published genome-wide association studies

Getting information: SIFT & PolyPhen

- **SIFT**
  - SIFT predicts whether an amino acid substitution affects protein function
  - **Interpretation:** 1 (tolerated) to 0 (deleterious)

http://sift.jcvi.org/

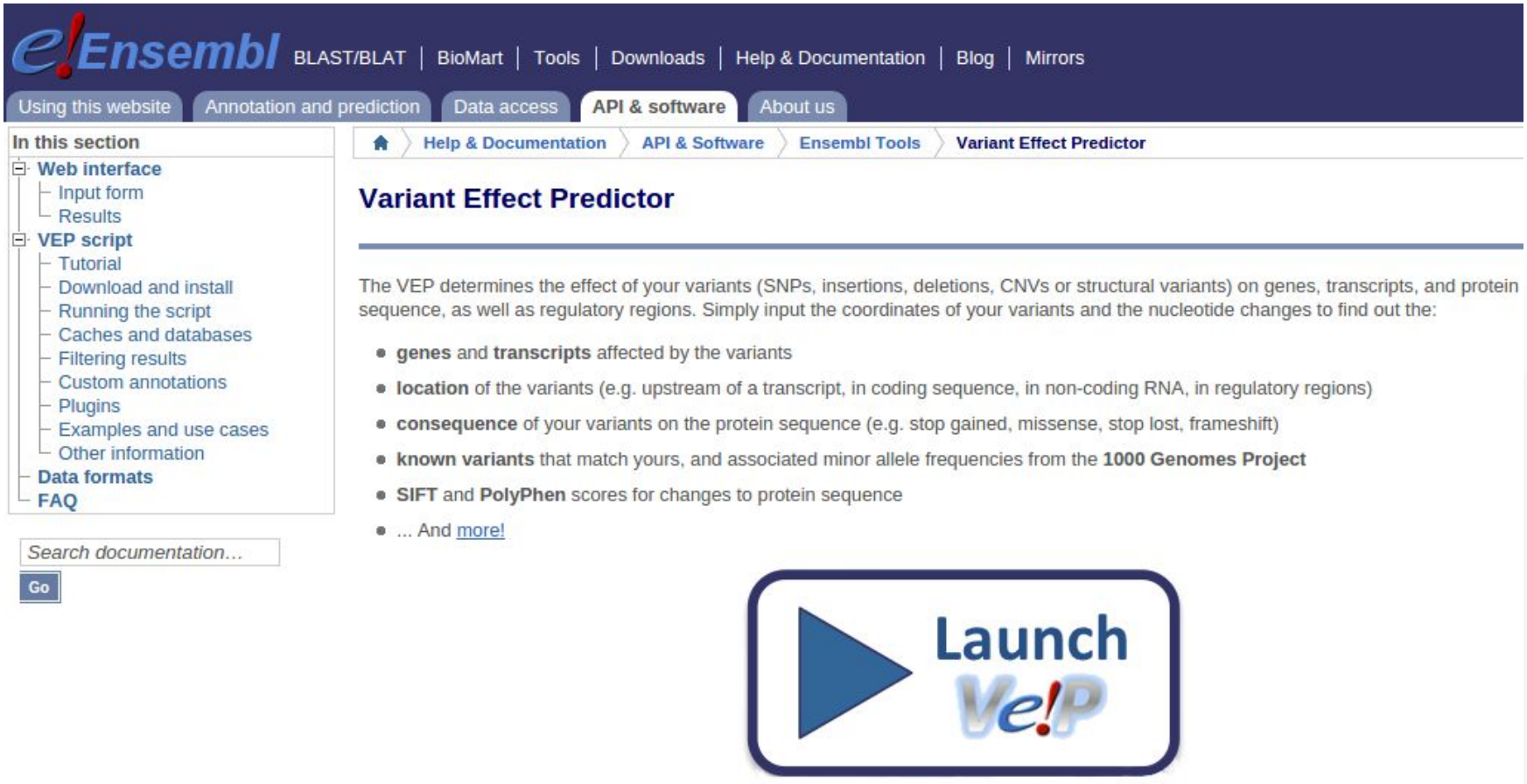
- **PolyPhen**
  - Polymorphism Phenotyping is a tool which predicts possible impact of an amino acid substitution on the structure and function of a human protein.
  - **Interpretation:** 1 (probably damage) to 0 (bening)

http://genetics.bwh.harvard.edu/pph2/index.shtml

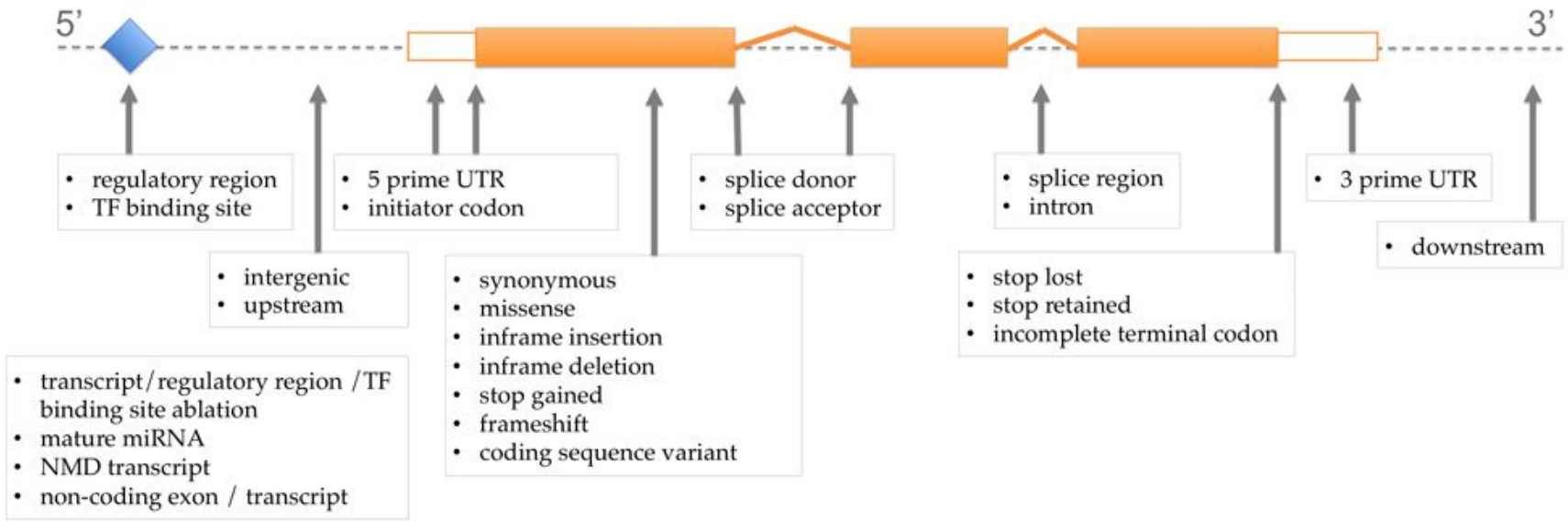
Getting information: Conservation

- **Phylop**
  - PhyloP scores measure evolutionary conservation at individual alignment sites. The scores are interpreted as follows compared to the evolution expected under neutral drift:
    - Positive scores -- Measure conservation, which is slower evolution than expected, at sites that are predicted to be conserved.
    - Negative scores -- Measure acceleration, which is faster evolution than expected, at sites that are predicted to be fast-evolving.
- **PhastCons**
  - PhastCons is a program for identifying evolutionarily conserved elements in a multiple alignment, given a phylogenetic tree.
  - PhastCons essentially does three things:
    - It produces base-by-base conservation scores (as displayed in the conservation tracks in the UCSC browser)
    - It produces predictions of discrete conserved elements (as displayed in the "most conserved" tracks in the browser)
    - It estimates free parameters.

Getting information: Effect



Getting information: Effect



http://www.ensembl.org/info/genome/variation/predicted_data.html

Inputs: Panel + VCF

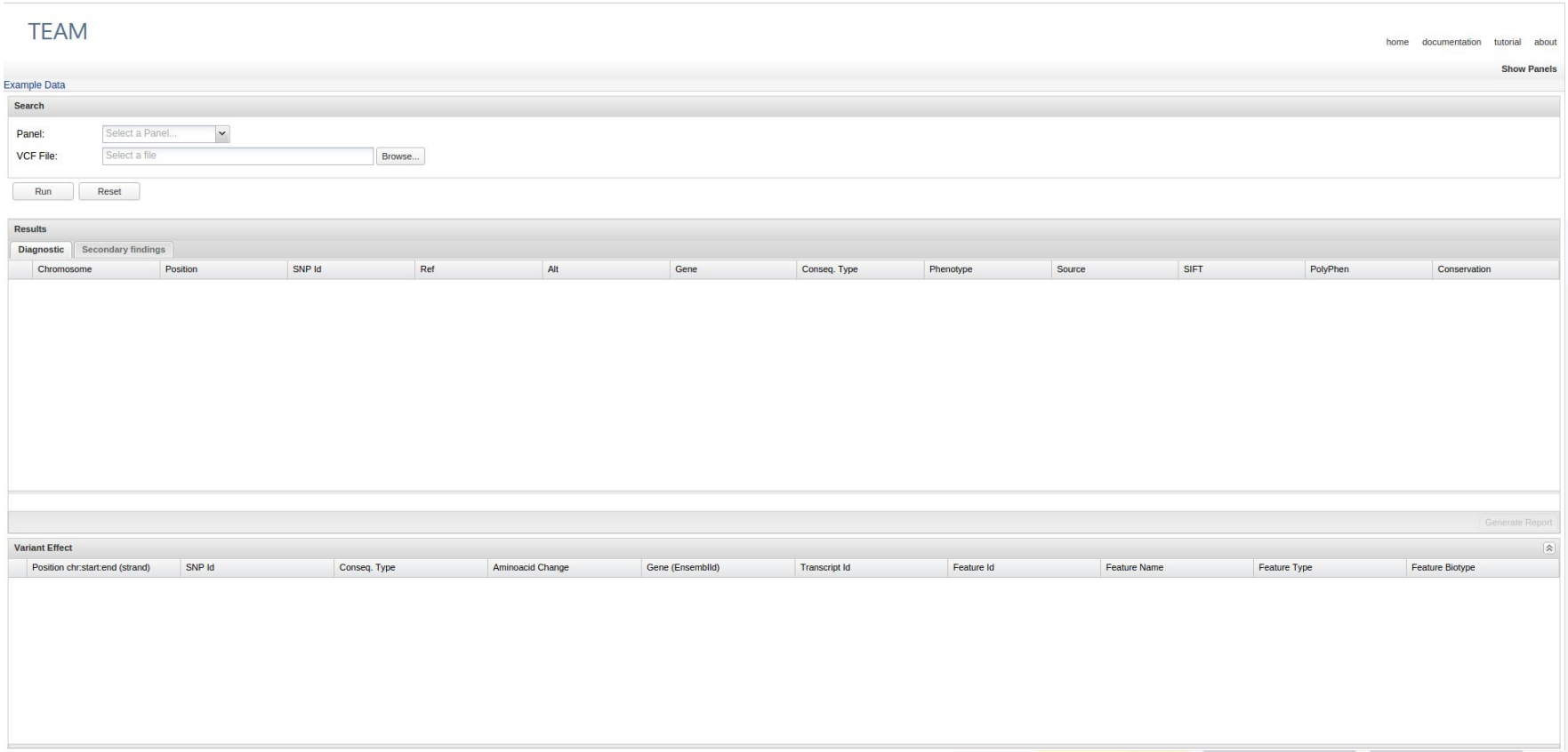
TEAM needs a:

1. **VCF file**:
   - The VCF file needs to be stored/indexed in our database.
   - This file could be already added if we used BiERapp (both tools are compatible)

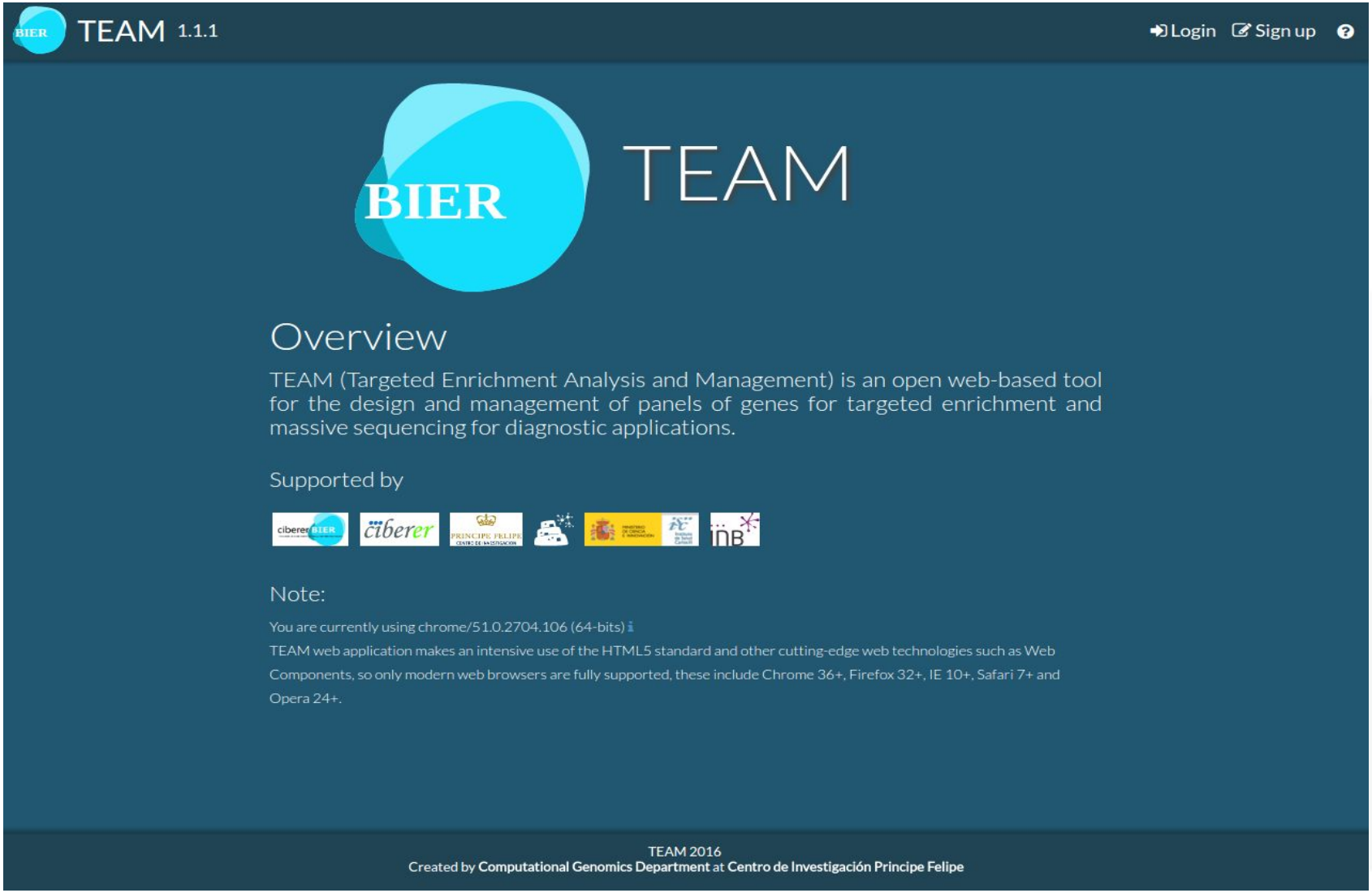
2. **Panel of genes**:
   - TEAM works with virtual panel of genes.
   - You can design/create/manage these panels using TEAM.
   - These panels contains:
     - Phenotypes
     - Genes
     - Mutations

Tool interface: Official release

http://team.babelomics.org/



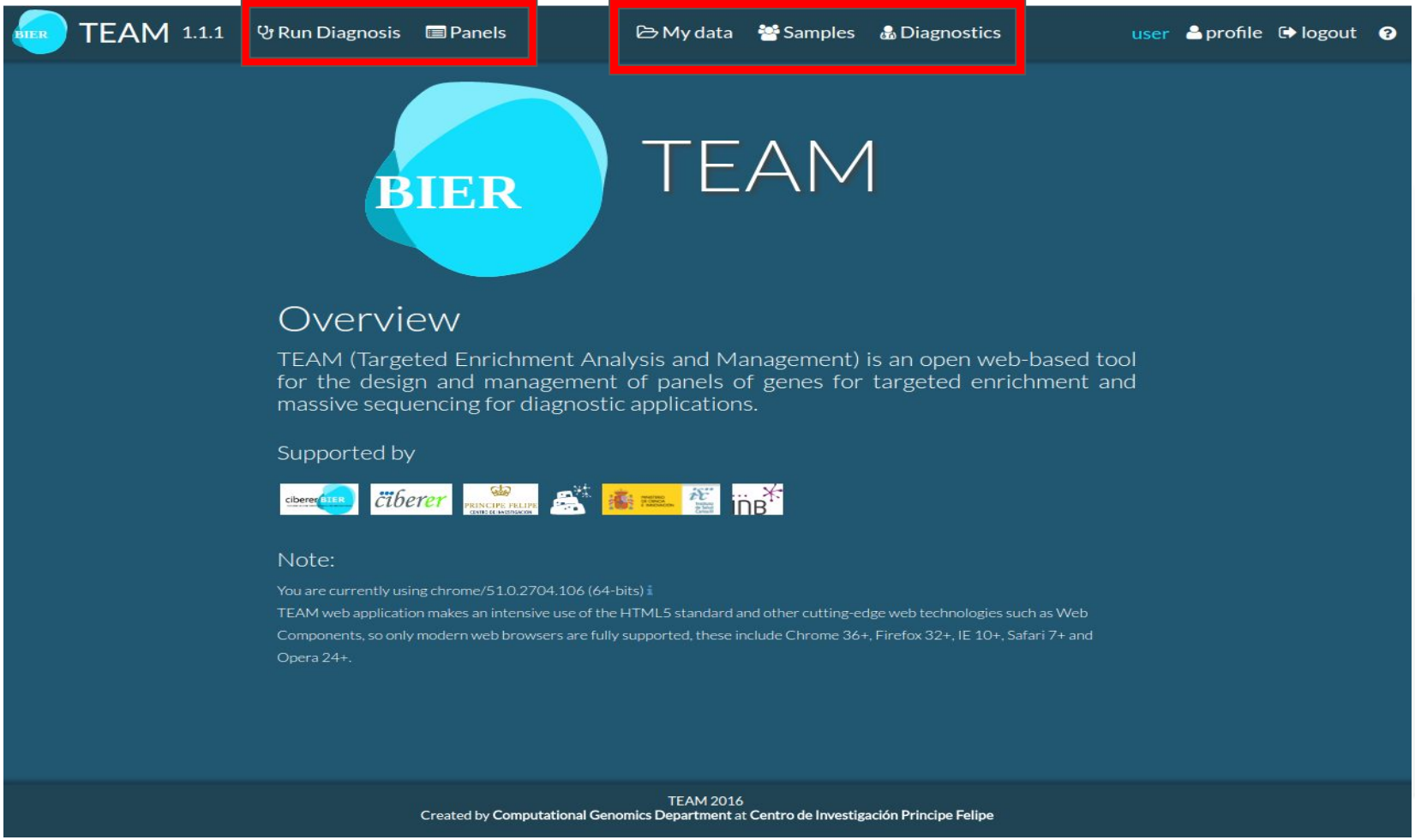
Tool interface: Beta



Tool interface: Beta

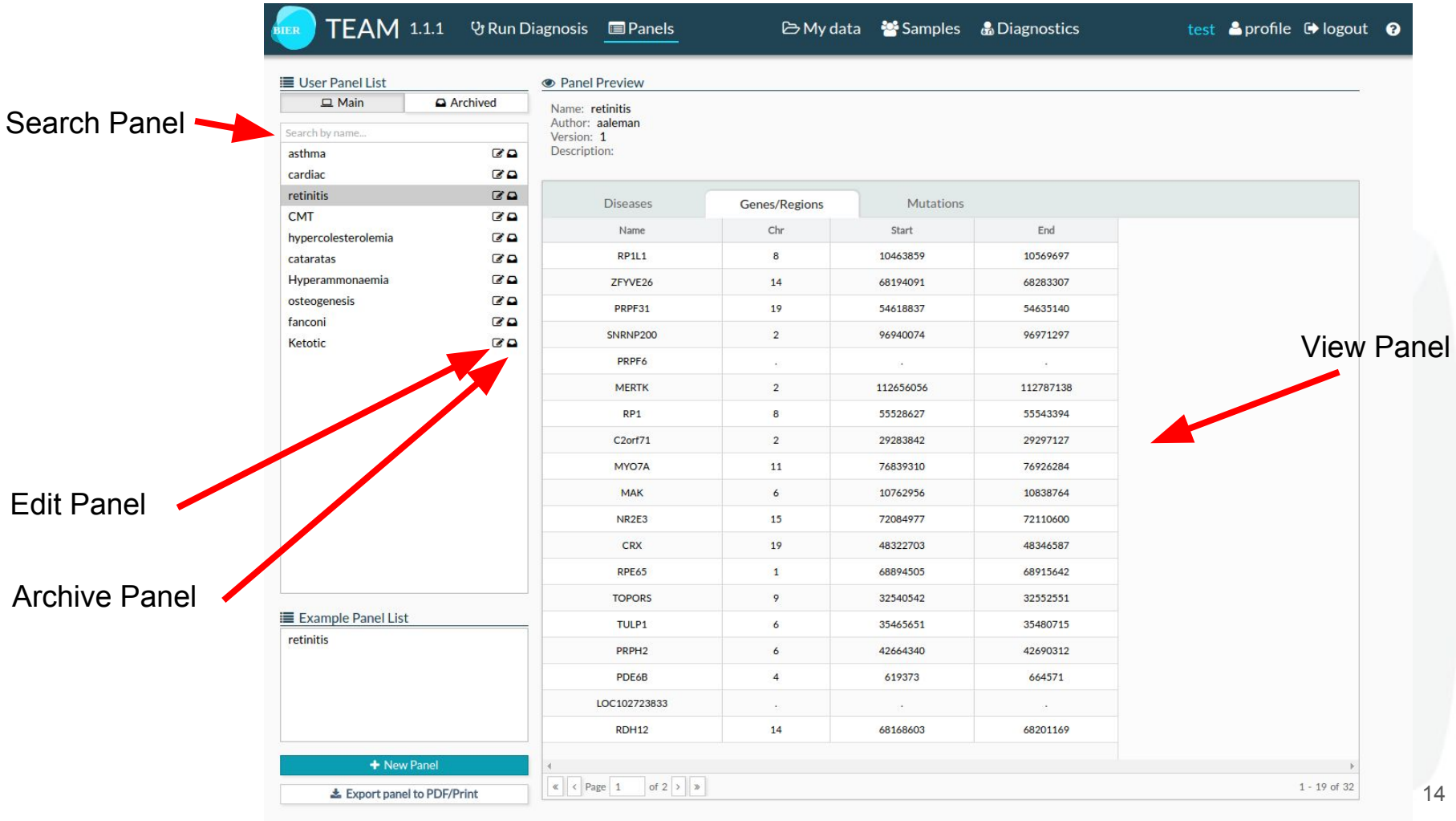
Design/Manage Panels

Data & Diagnoses

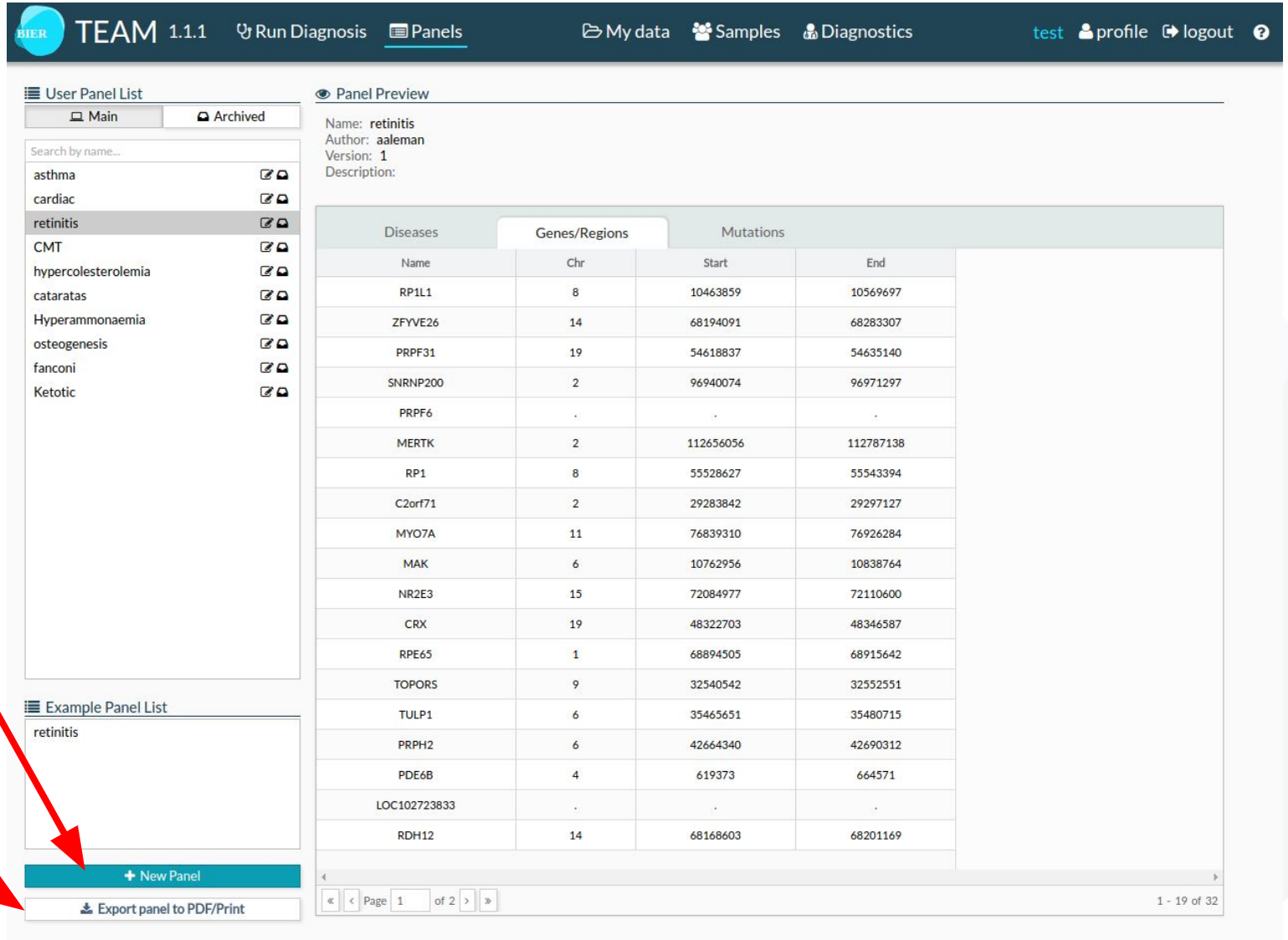


Panel Manager

You can manage your panels using “Panels”



Panel Manager: Create a Panel

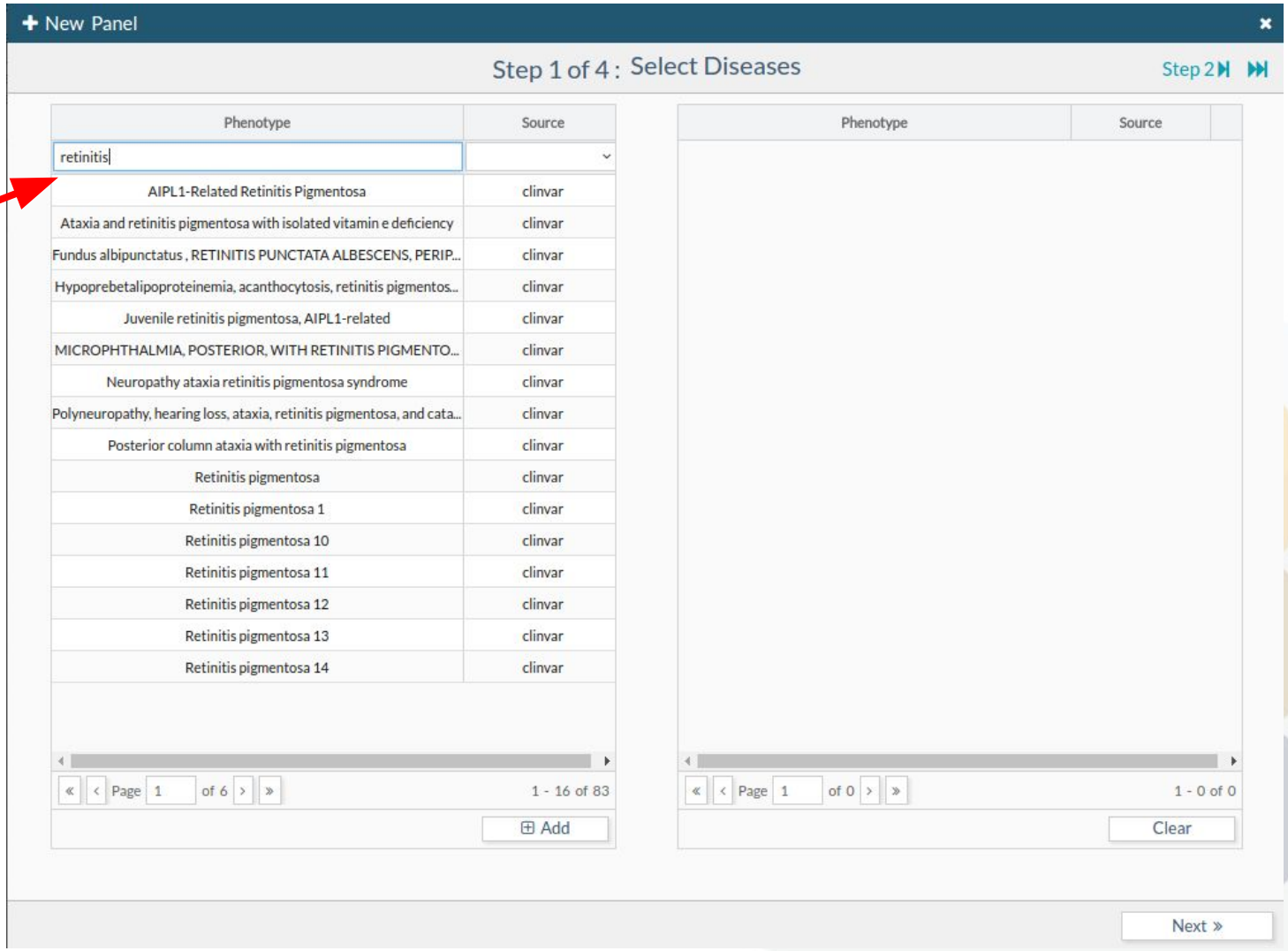


Create a New Panel

Export or Print a Panel

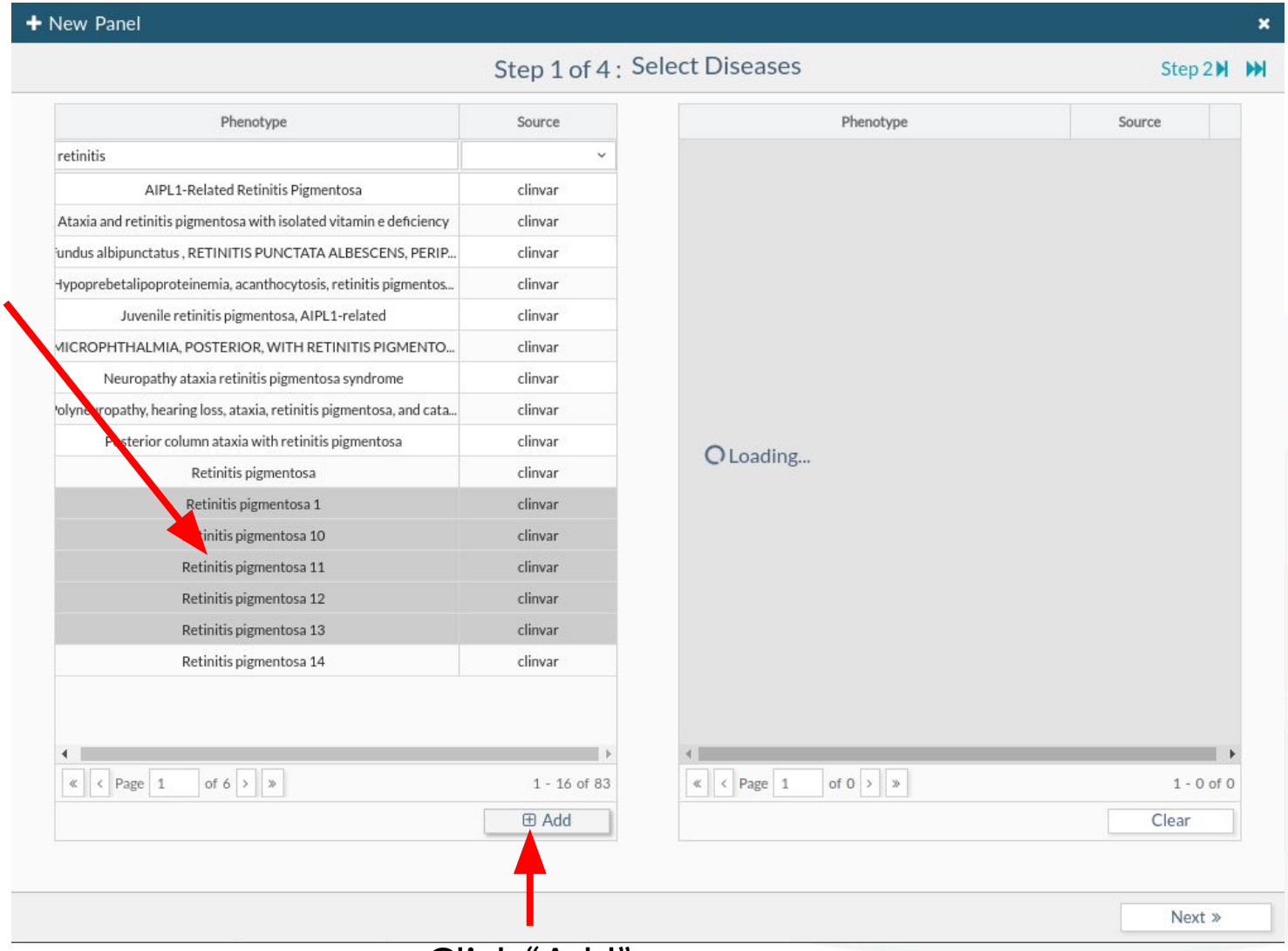
Panel Designer: Diseases

Write the phenotypes you are interested in.



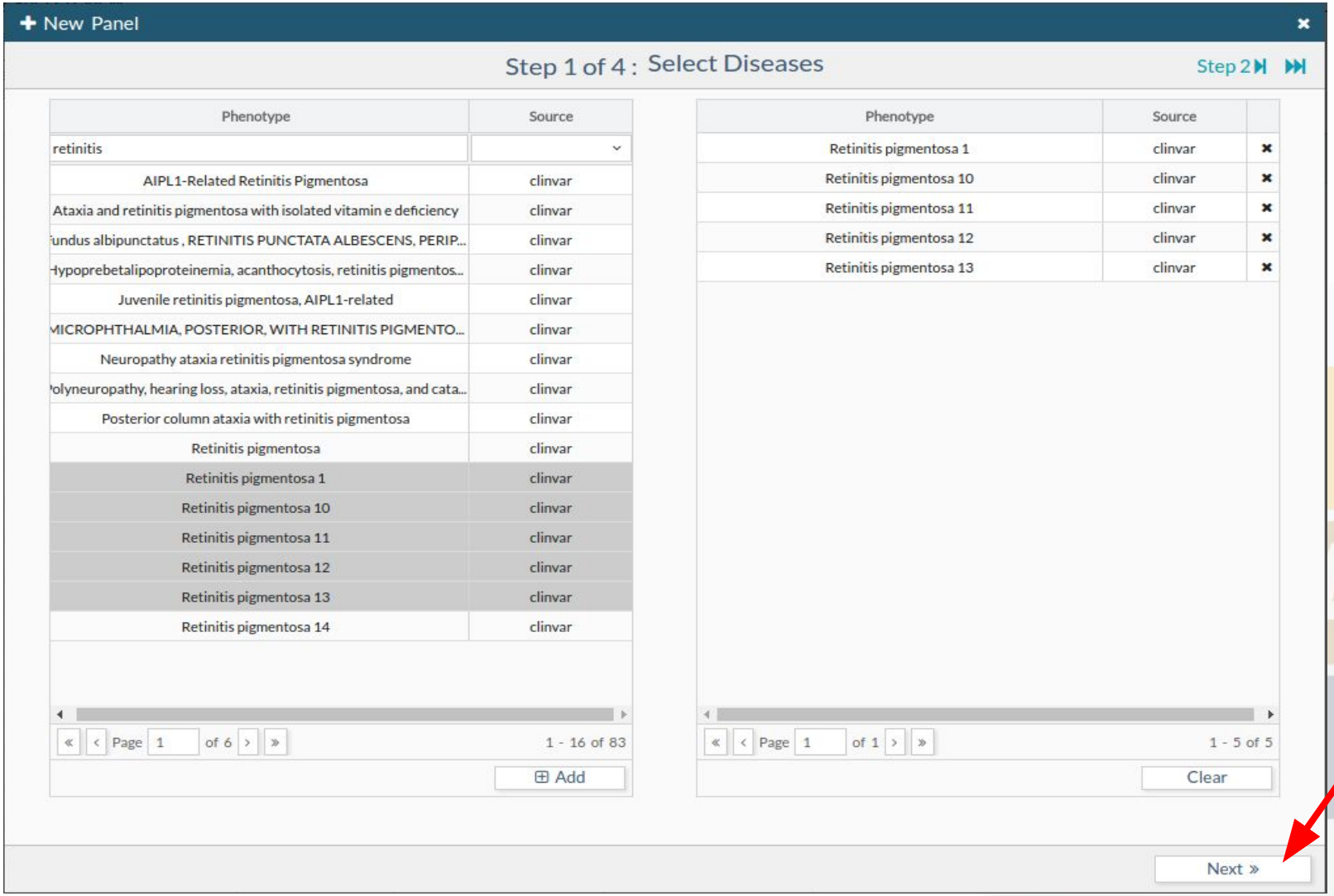
Panel Designer: Diseases

Select the phenotypes you want to add to the virtual panel. That will add the associated genes and mutations



Click “Add”

Panel Designer: Diseases

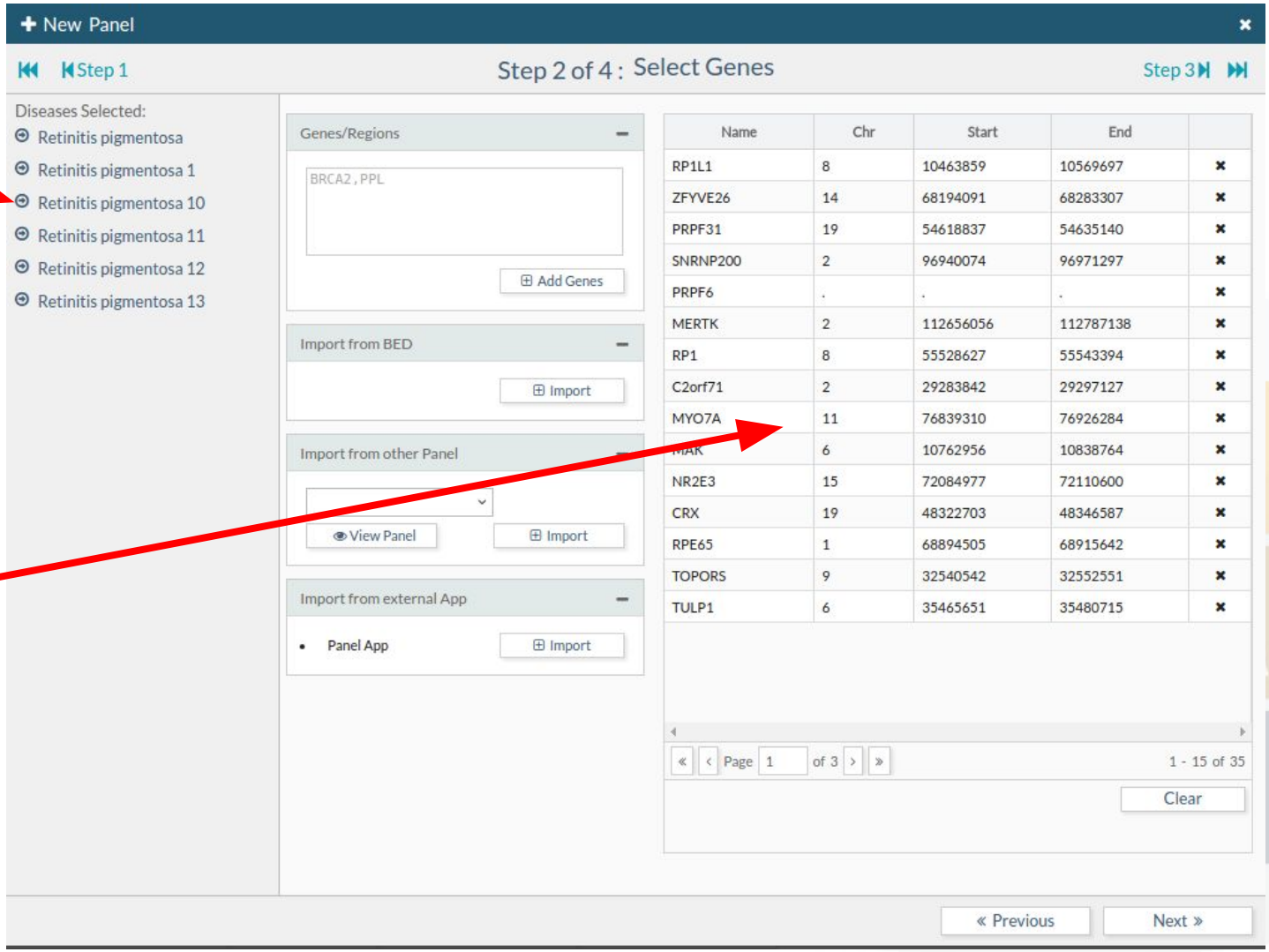


Next Step

Panel Designer: Genes

Selected Diseases in previous step.

These genes have been added by previous step.
These genes are related to the selected diseases

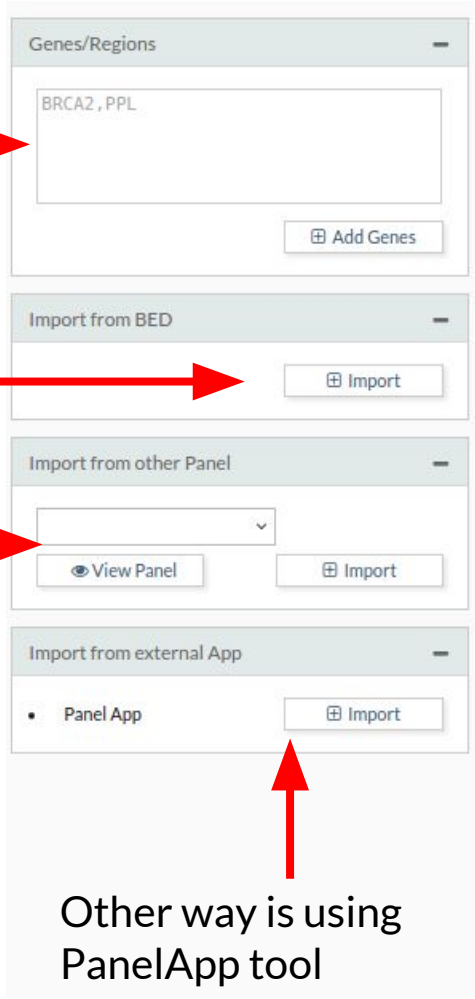


Panel Designer: Genes

We can add new genes typing the name or the region.

Adding regions through a BED file is also supported

We can import genes from other virtual panels already created.



Name	Chr	Start	End	
RP1L1	8	10463859	10569697	✖
ZFYVE26	14	68194091	68283307	✖
PRPF31	19	54618837	54635140	✖
SNRNP200	2	96940074	96971297	✖
PRPF6	.	.	.	✖
MERTK	2	112656056	112787138	✖
RP1	8	55528627	55543394	✖
C2orf71	2	29283842	29297127	✖
MYO7A	11	76839310	76926284	✖
MAK	6	10762956	10838764	✖
NR2E3	15	72084977	72110600	✖
CRX	19	48322703	48346587	✖
RPE65	1	68894505	68915642	✖
TOPORS	9	32540542	32552551	✖
TULP1	6	35465651	35480715	✖

« ‹ Page 1 of 3 › » 1 - 15 of 35

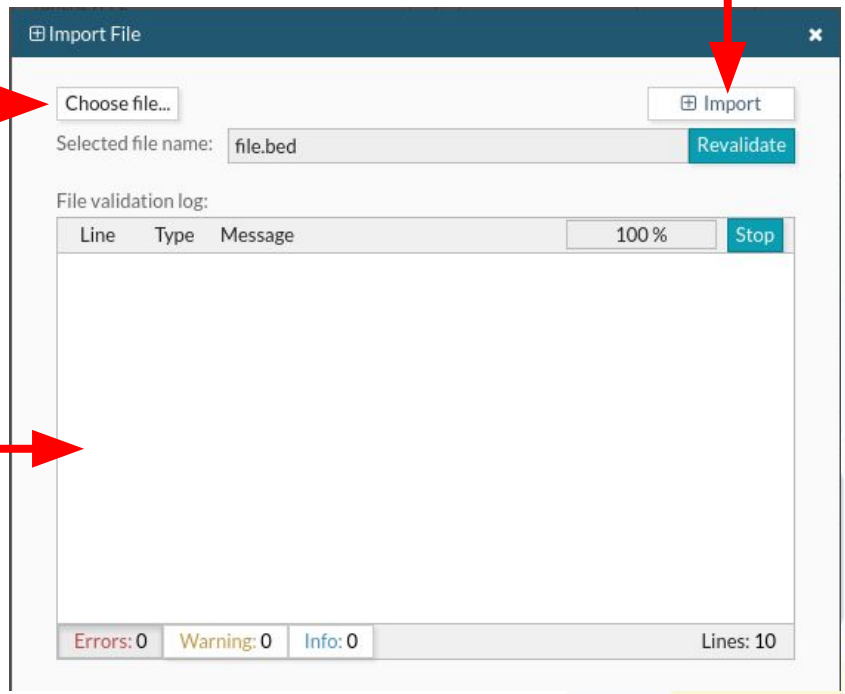
Clear

Other way is using PanelApp tool

Panel Designer: Genes (BED file)

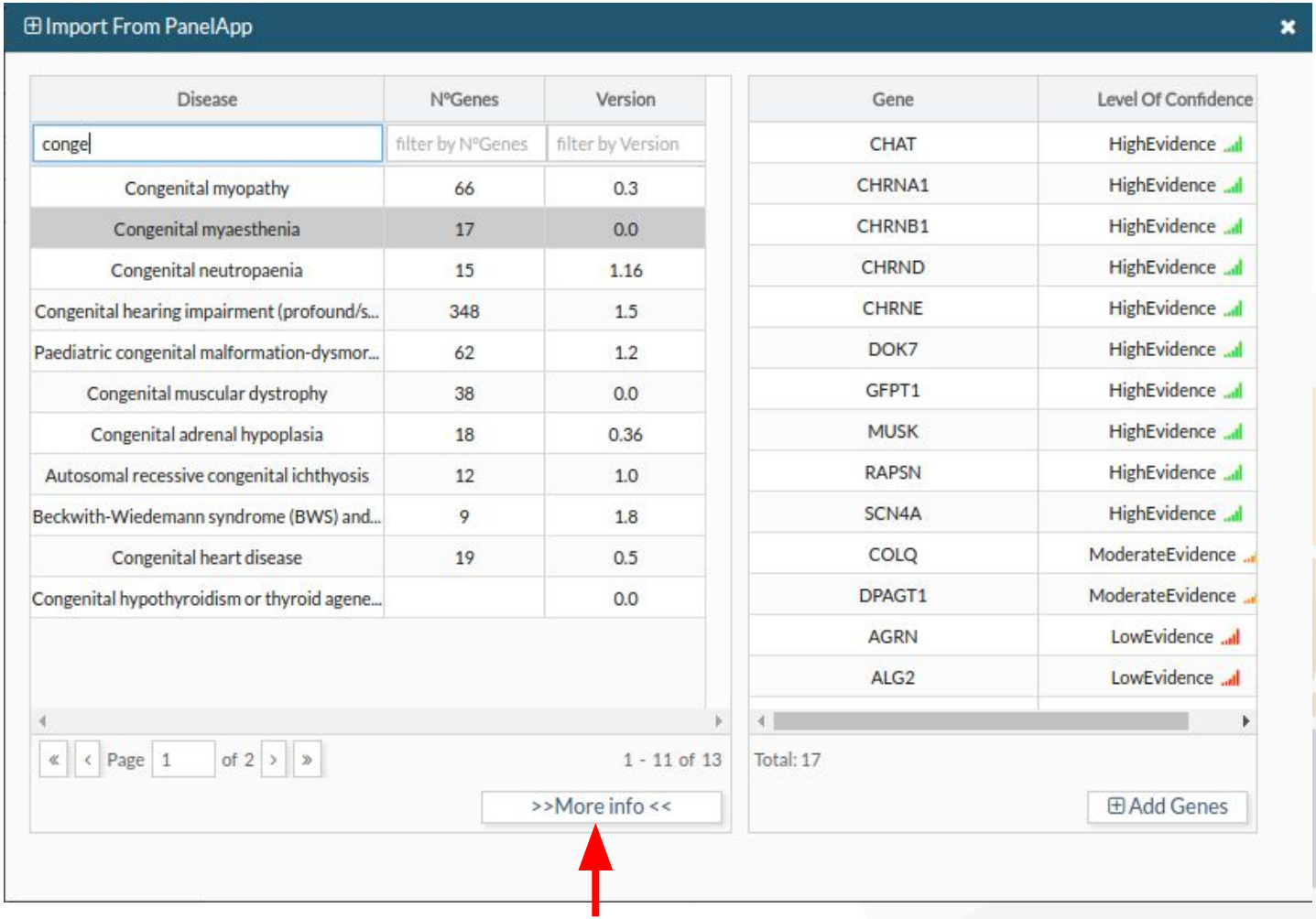
Import genes

Choose a BED file



Check errors or warnings

Panel Designer: Genes (PanelApp)



https://bioinfo.extge.co.uk/crowdsourcing/PanelApp/

Panel Designer: Genes (PanelApp)

Genomics England PanelApp

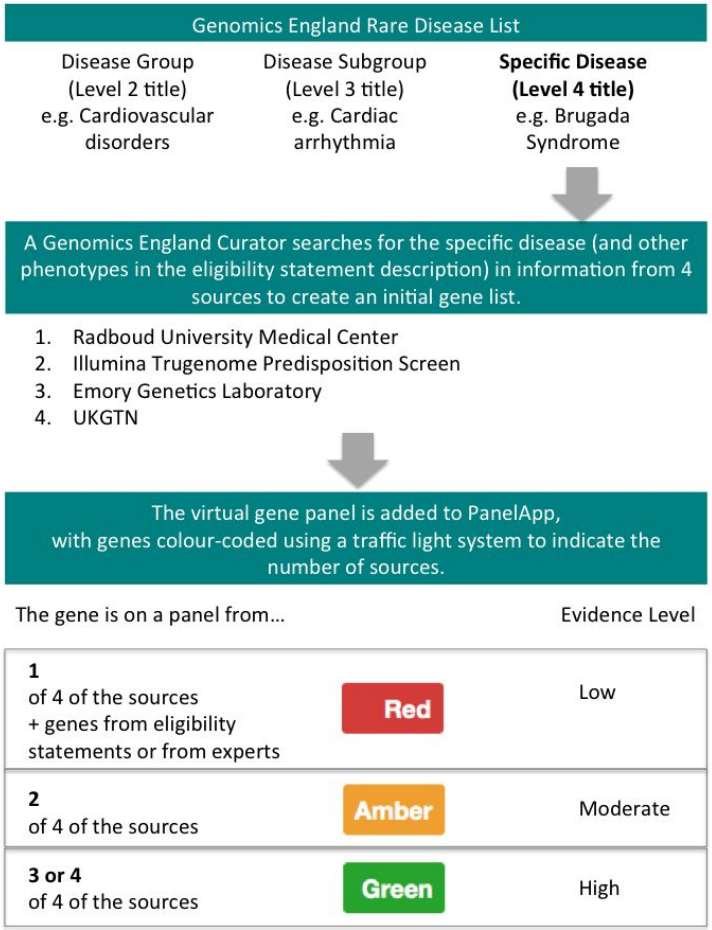
A crowdsourcing tool to allow gene panels to be shared, downloaded, viewed and evaluated by the Scientific Community

Reviews are assessed by Genomics England Curators to establish a final virtual gene panel

Each gene is either…	Evidence Level
Green	High, diagnostic-grade gene that will be used to Interpret genomes.
Red	Low/moderate evidence, genes that currently cannot be used to report clinically, more evidence may arise in the future.

https://bioinfo.extge.co.uk/crowdsourcing/PanelApp/

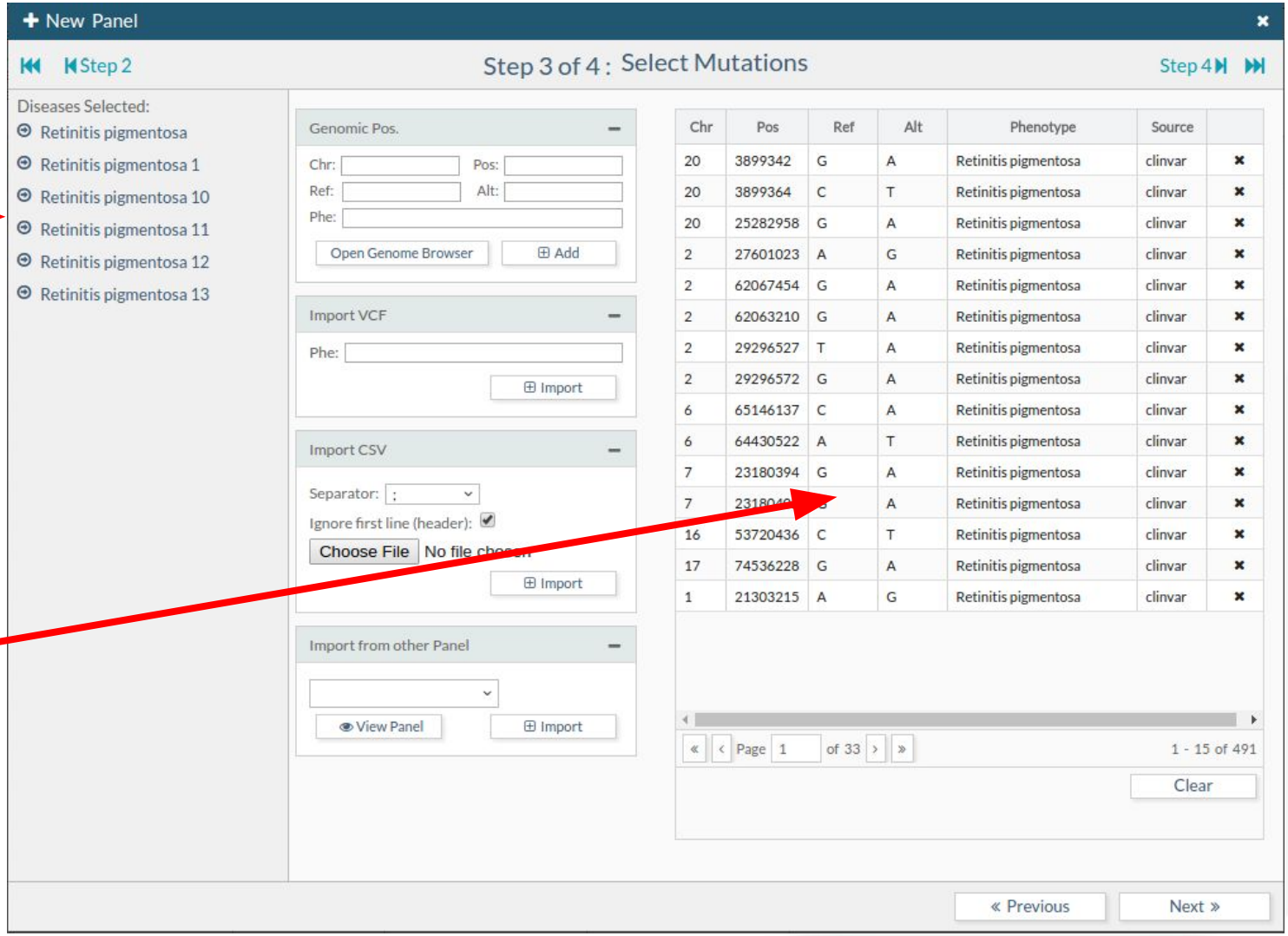
Figure 1: The curation process for the initial establishment of gene panels for each rare disease category



Panel Designer: Mutations

Selected Diseases in previous step.

These mutations have been added by the first step. They are related to the selected diseases

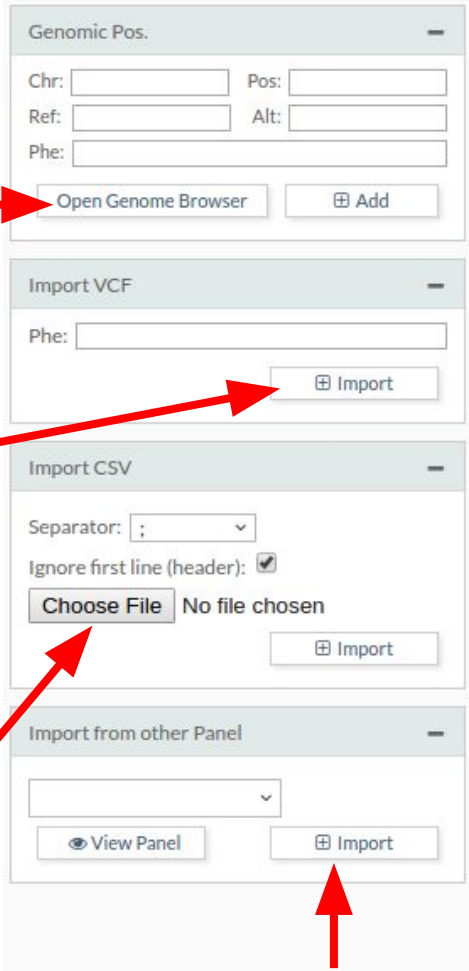


Panel Designer: Mutations

We add our custom mutations by writing the genomic position and the change (ref-alt).
Or we can use the Genome Browser to find the specific position

You can import mutations from a VCF file

Or you can import them from a CSV file with the next format:
CHR POS REF ALT PHE



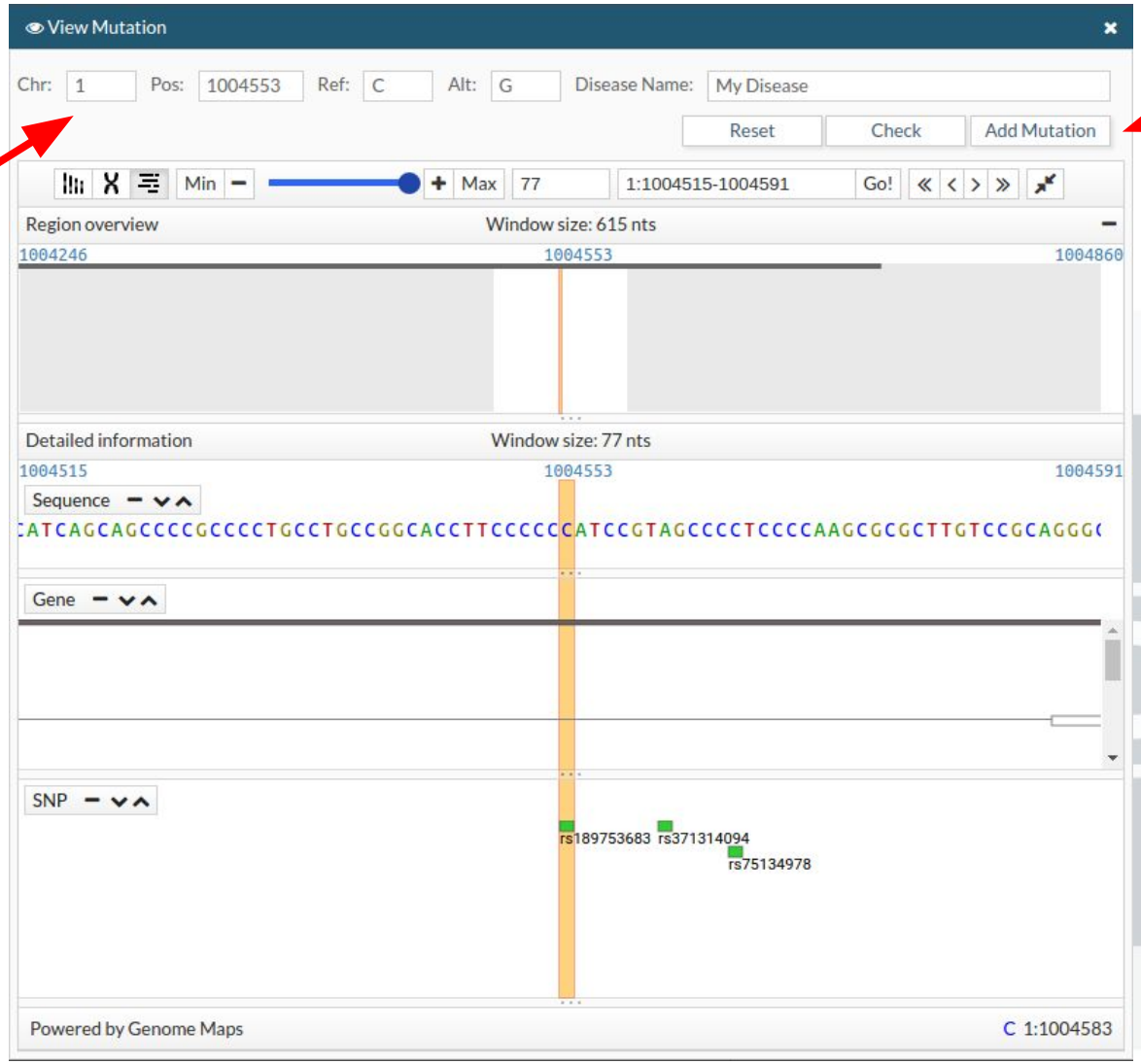
Chr	Pos	Ref	Alt	Phenotype	Source	
20	3899342	G	A	Retinitis pigmentosa	clinvar	✖
20	3899364	C	T	Retinitis pigmentosa	clinvar	✖
20	25282958	G	A	Retinitis pigmentosa	clinvar	✖
2	27601023	A	G	Retinitis pigmentosa	clinvar	✖
2	62067454	G	A	Retinitis pigmentosa	clinvar	✖
2	62063210	G	A	Retinitis pigmentosa	clinvar	✖
2	29296527	T	A	Retinitis pigmentosa	clinvar	✖
2	29296572	G	A	Retinitis pigmentosa	clinvar	✖
6	65146137	C	A	Retinitis pigmentosa	clinvar	✖
6	64430522	A	T	Retinitis pigmentosa	clinvar	✖
7	23180394	G	A	Retinitis pigmentosa	clinvar	✖
7	23180402	G	A	Retinitis pigmentosa	clinvar	✖
16	53720436	C	T	Retinitis pigmentosa	clinvar	✖
17	74536228	G	A	Retinitis pigmentosa	clinvar	✖
1	21303215	A	G	Retinitis pigmentosa	clinvar	✖

« ‹ Page 1 of 33 › » 1 - 15 of 491

Clear

Importing mutations from other virtual panels is supported too.

Panel Designer: Mutations



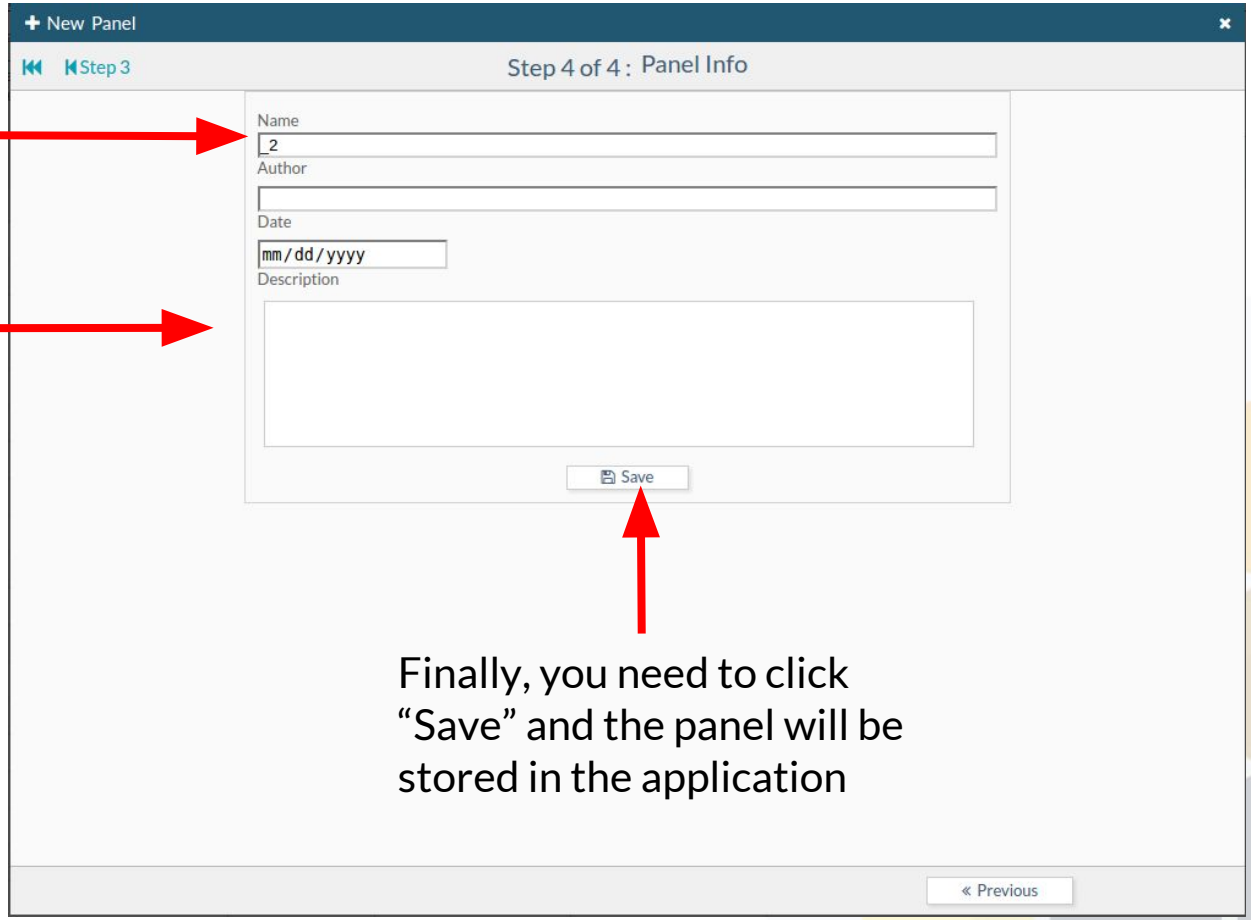
Import mutation

Search mutation

Panel Designer: Panel info

The name of the Panel

The author/ date/ description

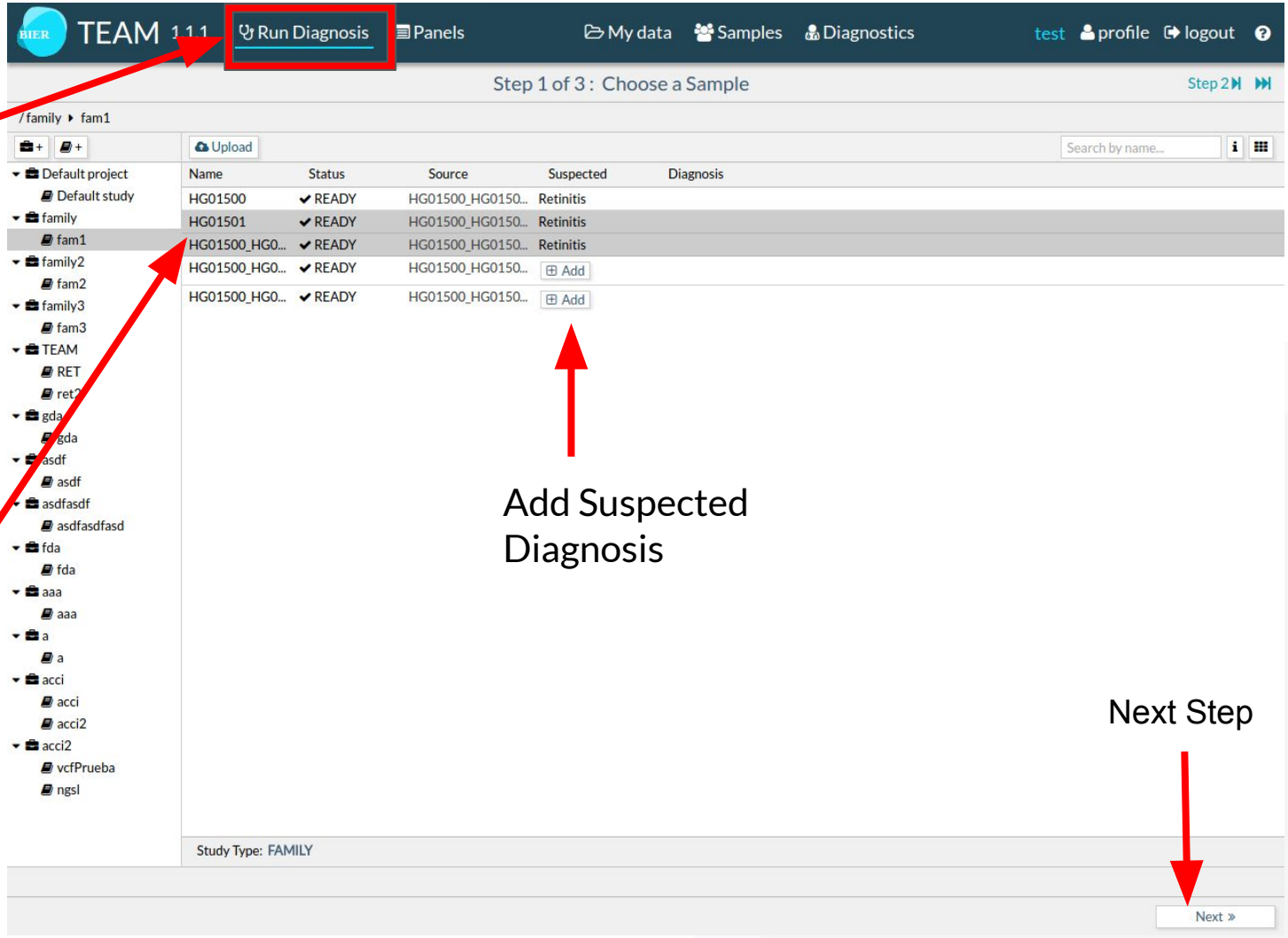


Finally, you need to click "Save" and the panel will be stored in the application

New Diagnosis

Click “Run Diagnosis”

Choose a Study. And then a sample/s in **Ready** status and with **Suspected diagnosis** added.

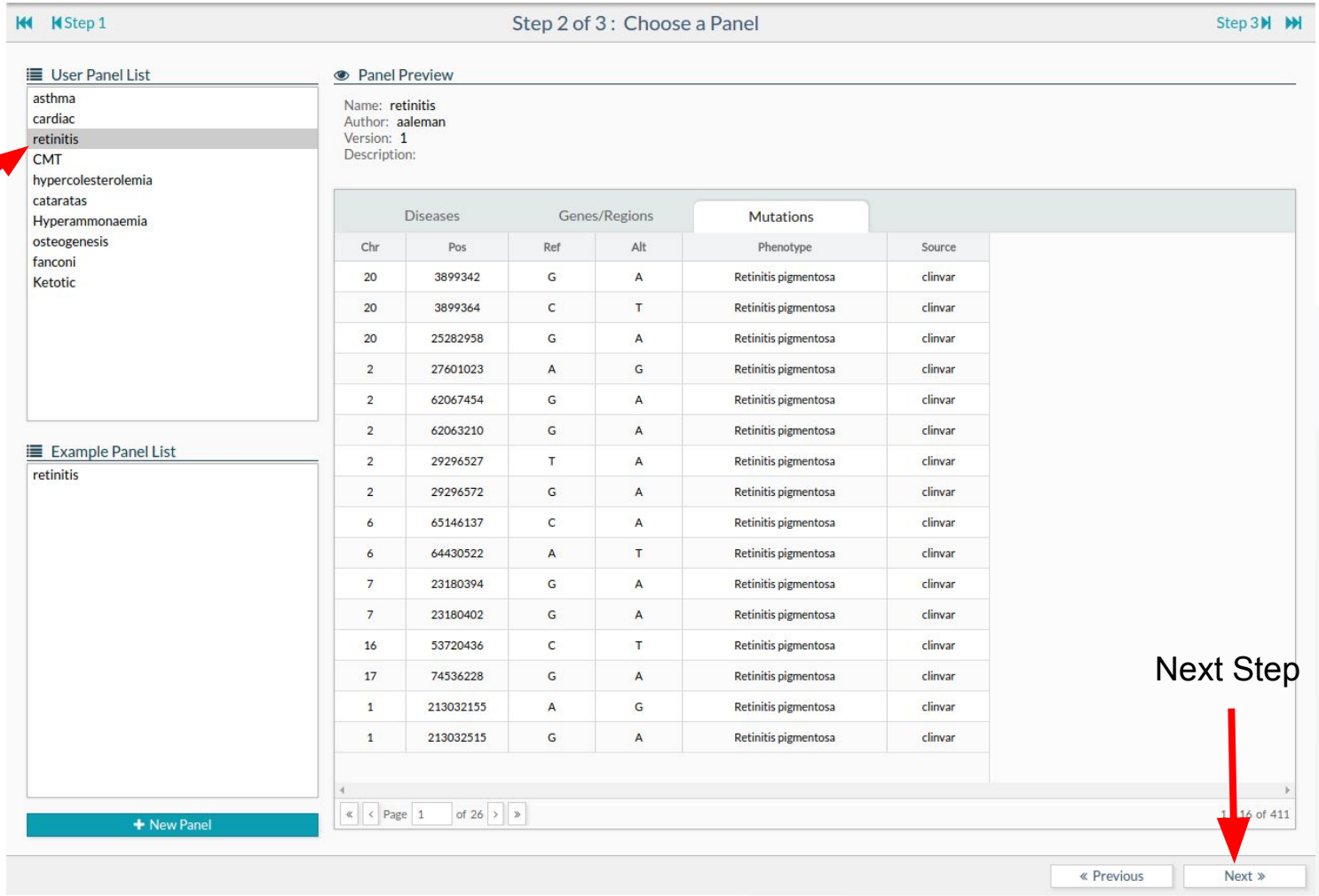


Add Suspected Diagnosis

Next Step

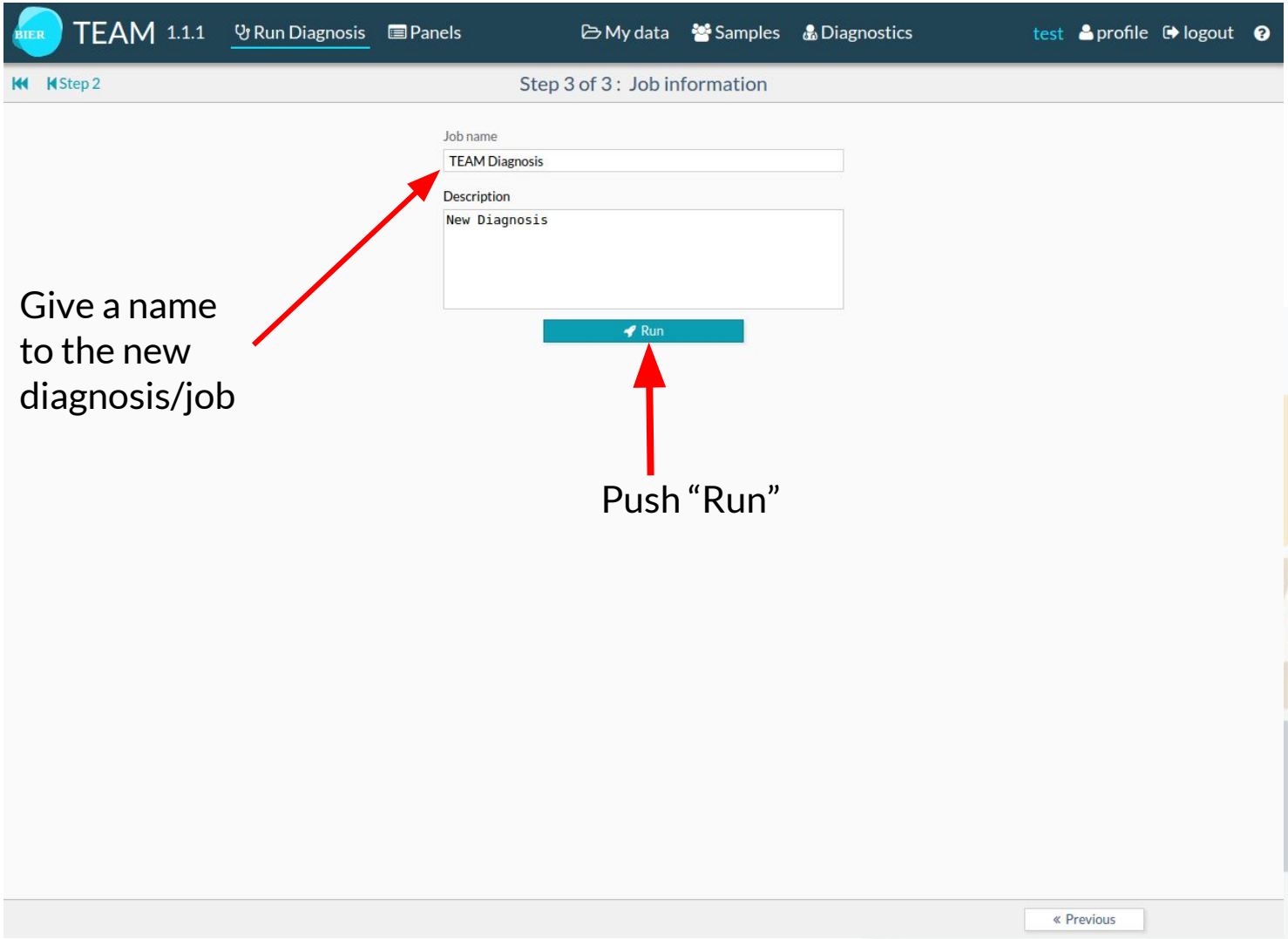
New Diagnosis

Select the panel to be used.



Next Step

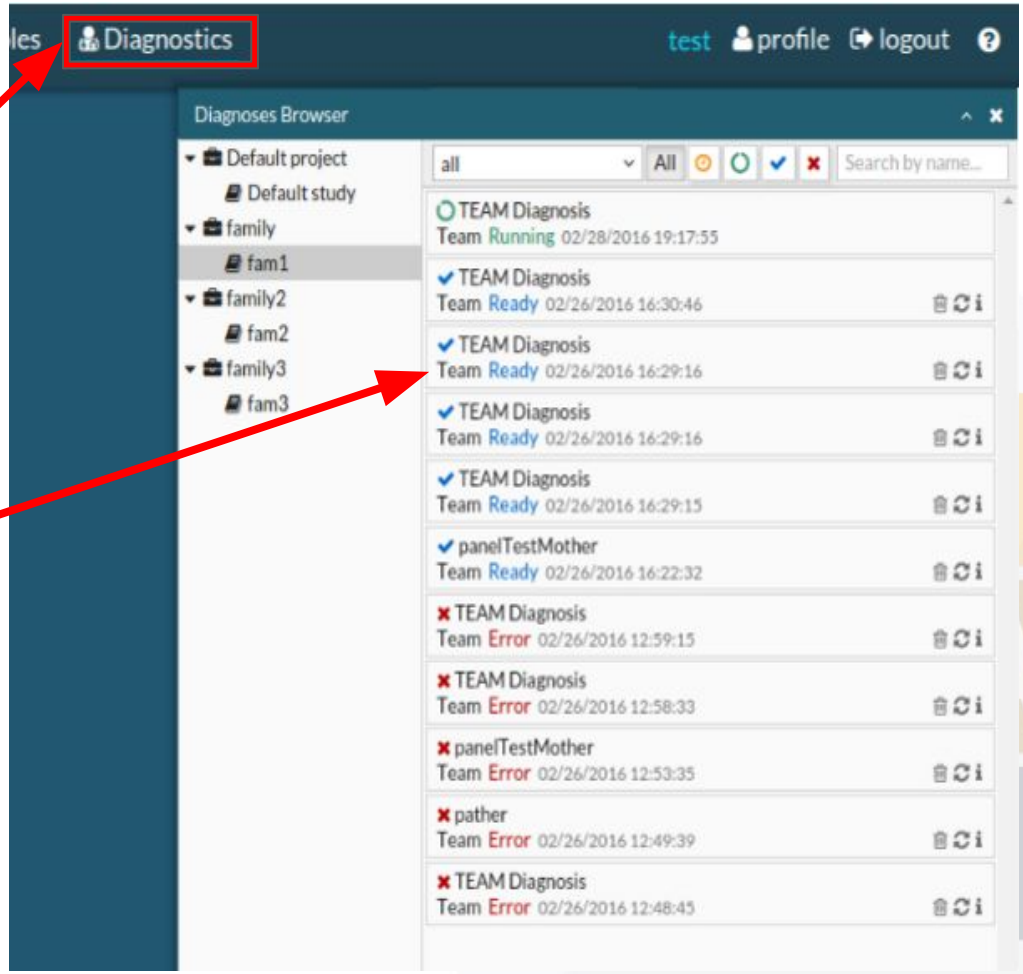
New Diagnosis



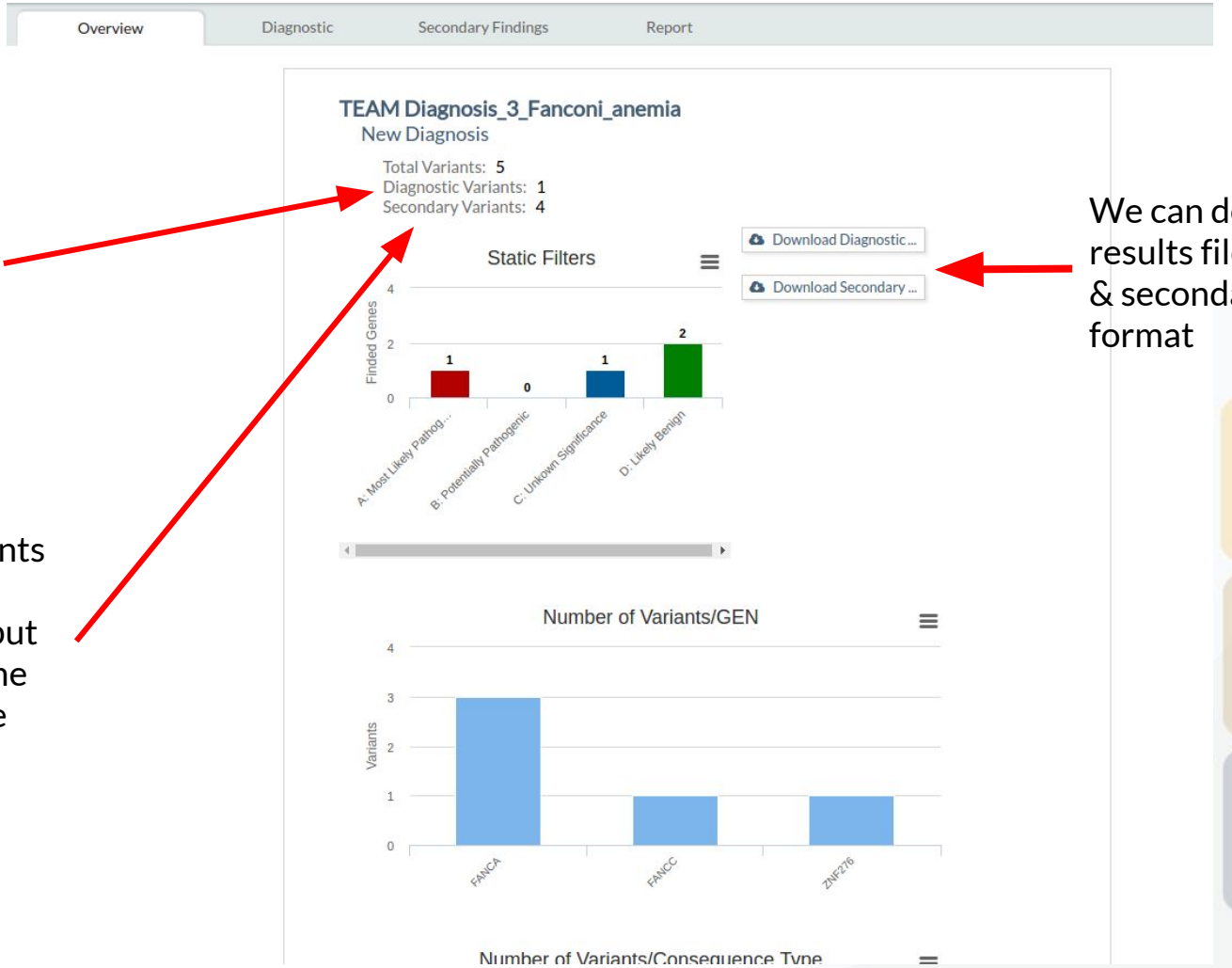
Diagnoses

This view shows the status of the current/past diagnoses.
The different status are: QUEUED, RUNNING, READY, ERROR

If you select a specific Diagnoses you will access to the results of that diagnoses.



Results: Overview

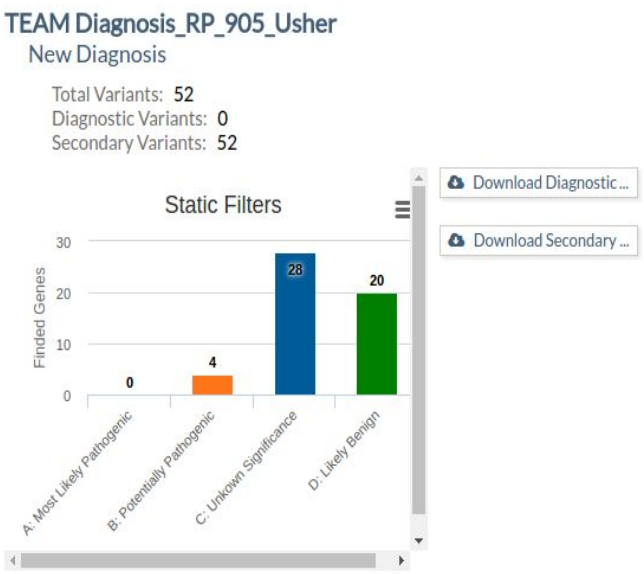


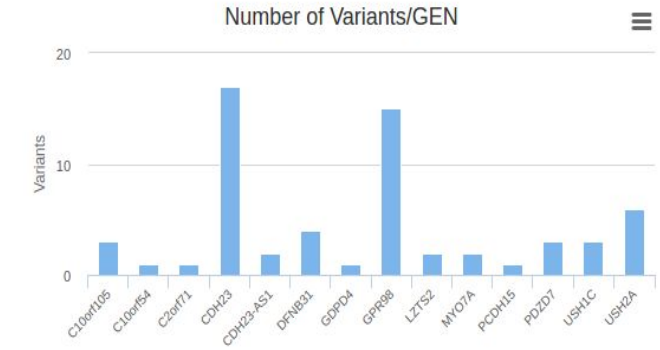
We got one diagnostic variant

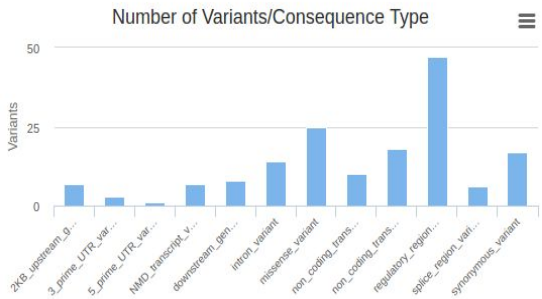
Secondary findings: 4
These variants are not diagnostic but are inside the genes of the panel

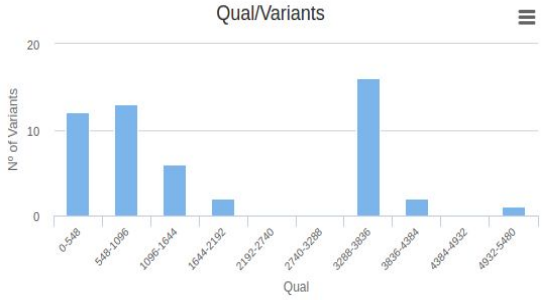
We can download the results files (diagnostic & secondary) in CSV format

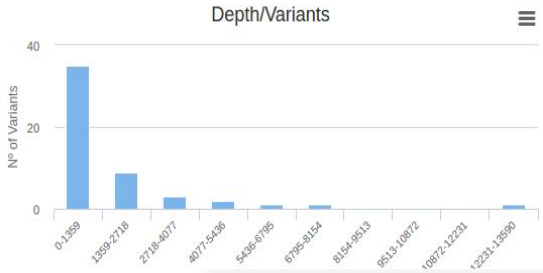
Results: Overview



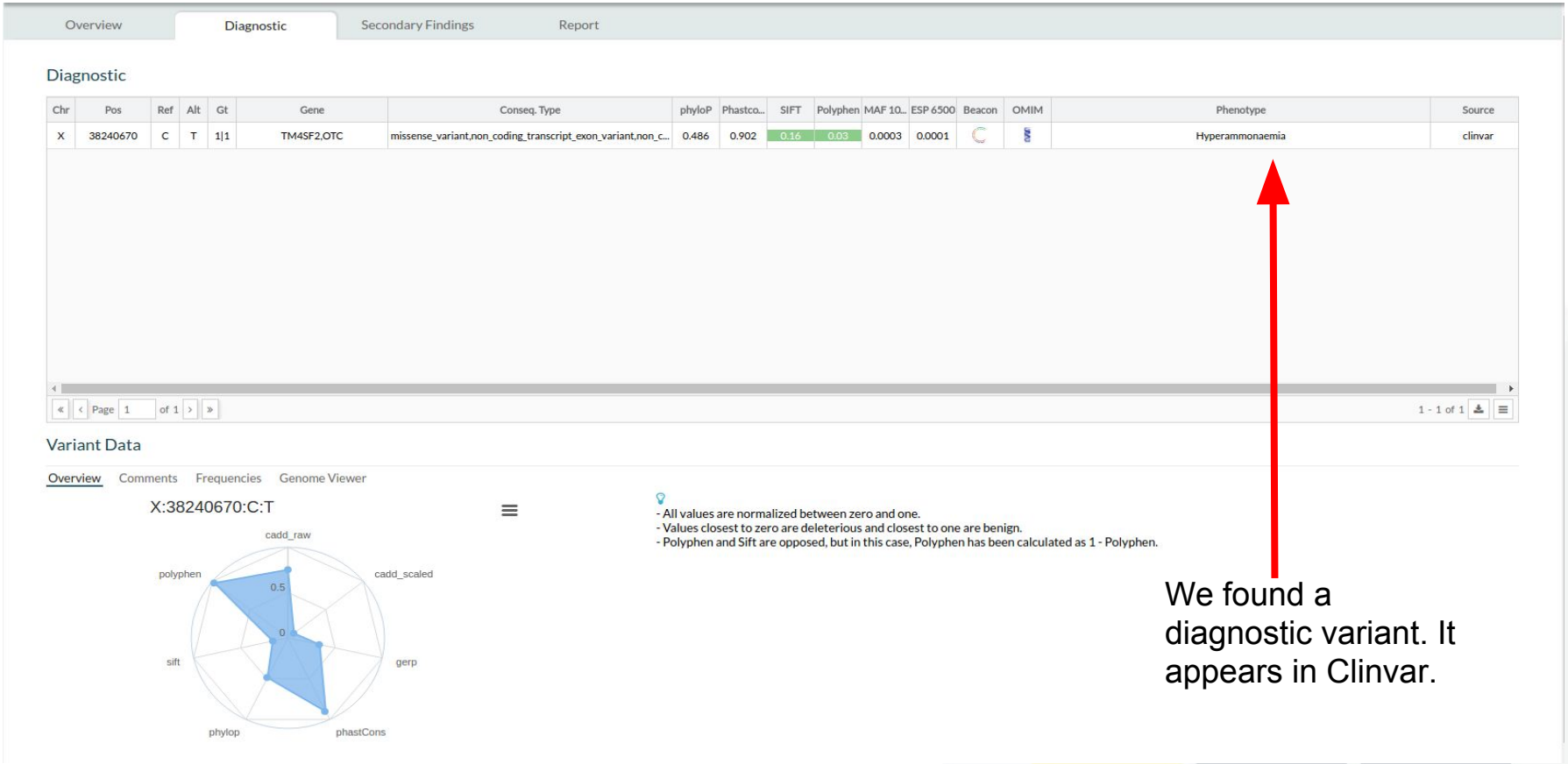








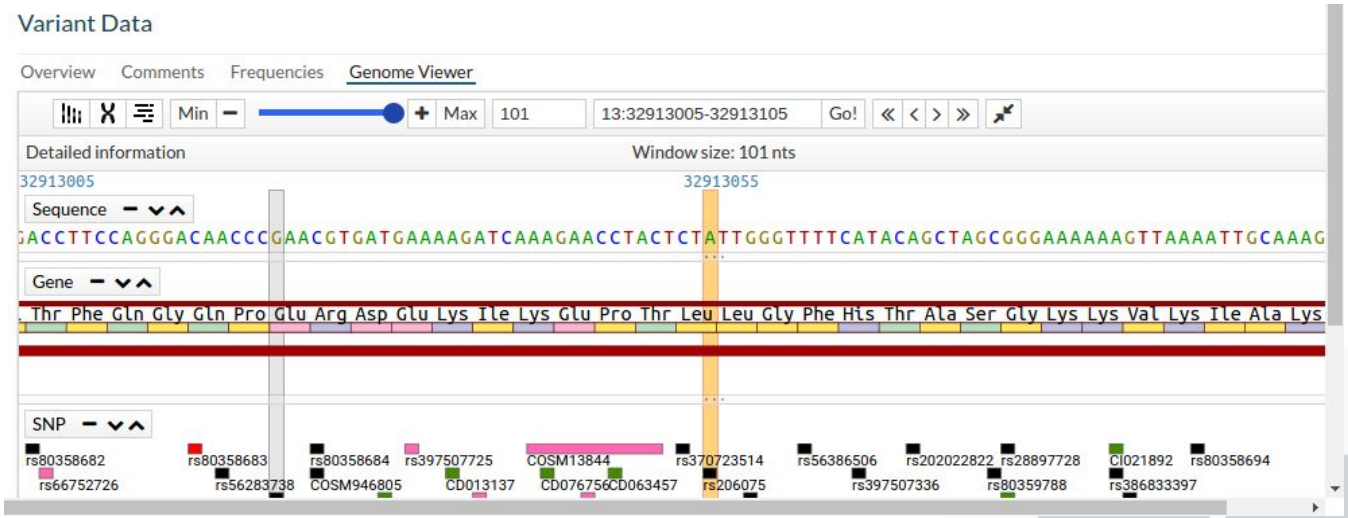
Results: Diagnostic Variants

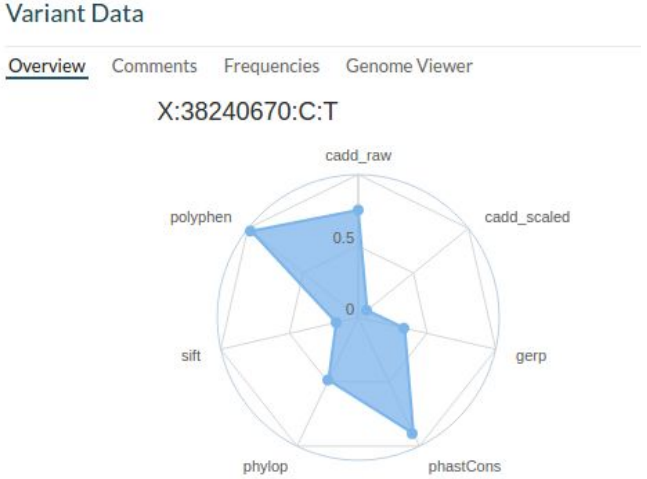


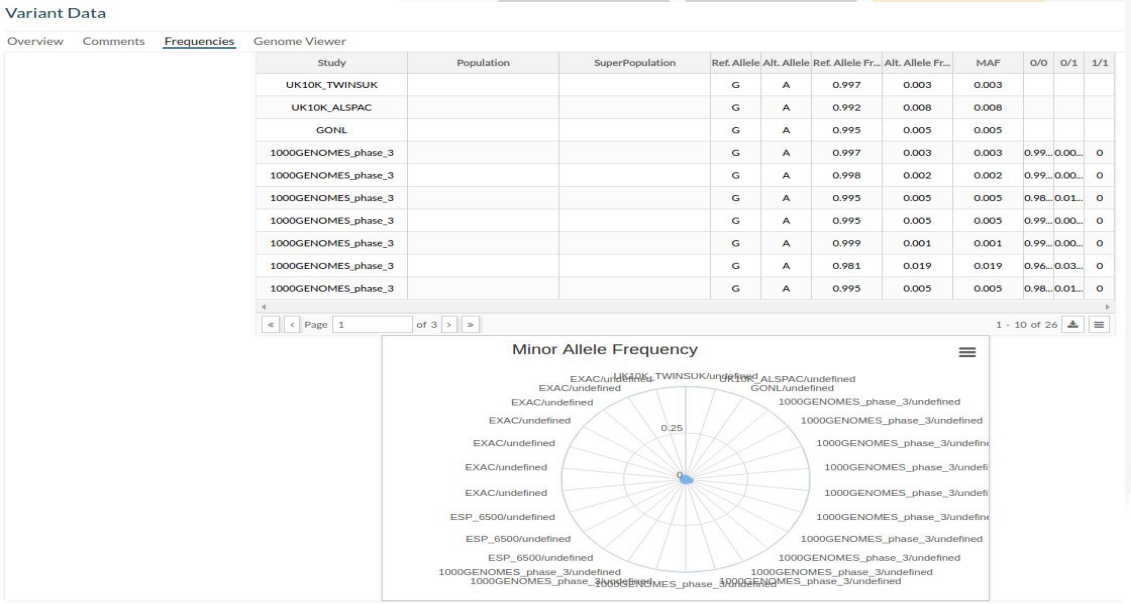
We found a diagnostic variant. It appears in Clinvar.

These are the variants in our sample that are within the regions and appear in the list of mutations of our panel.

Results: Variant Data

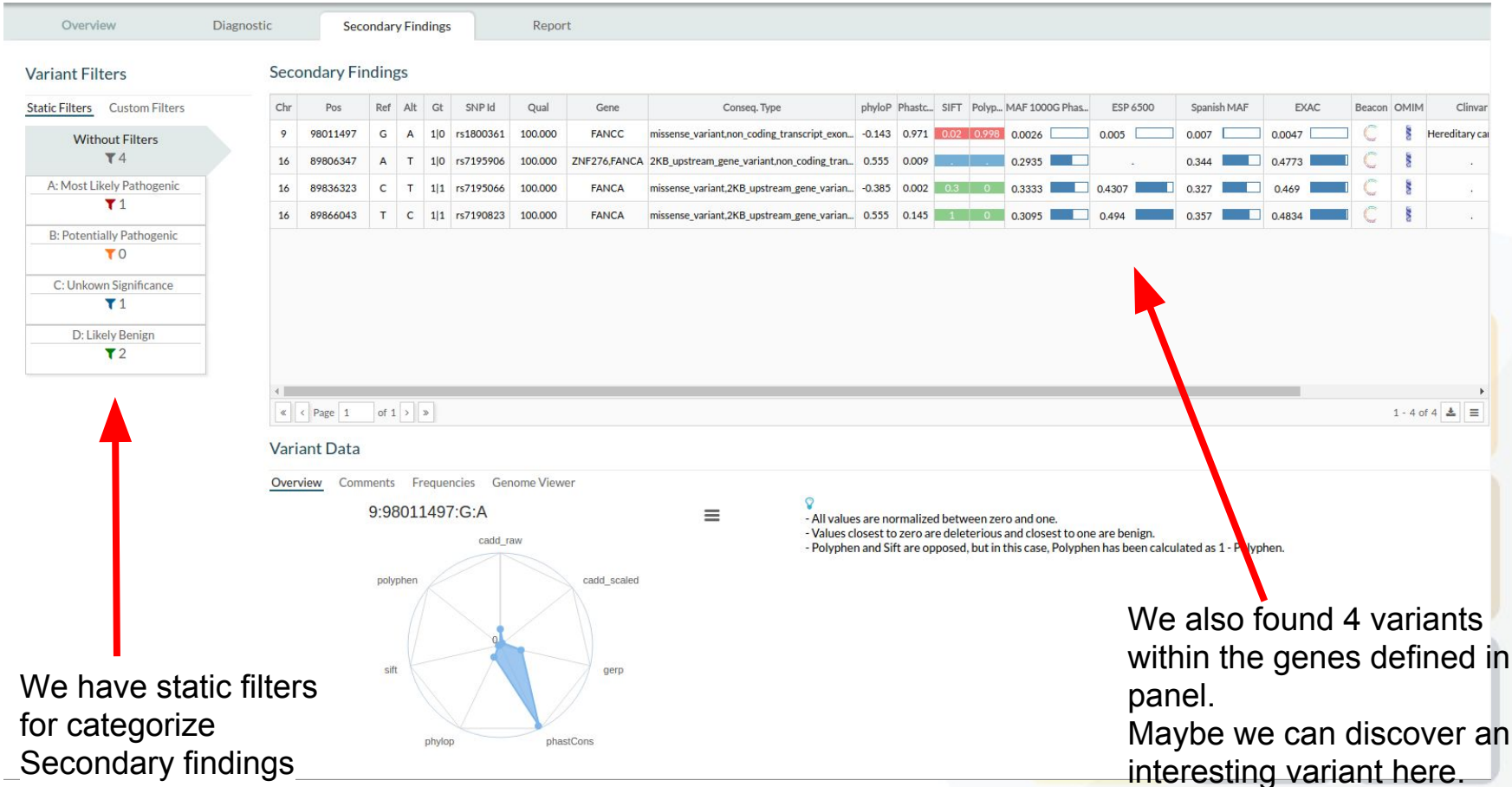






Results: Secondary Findings

These are the variants that are within the regions of our panel, but not in the list of mutations.



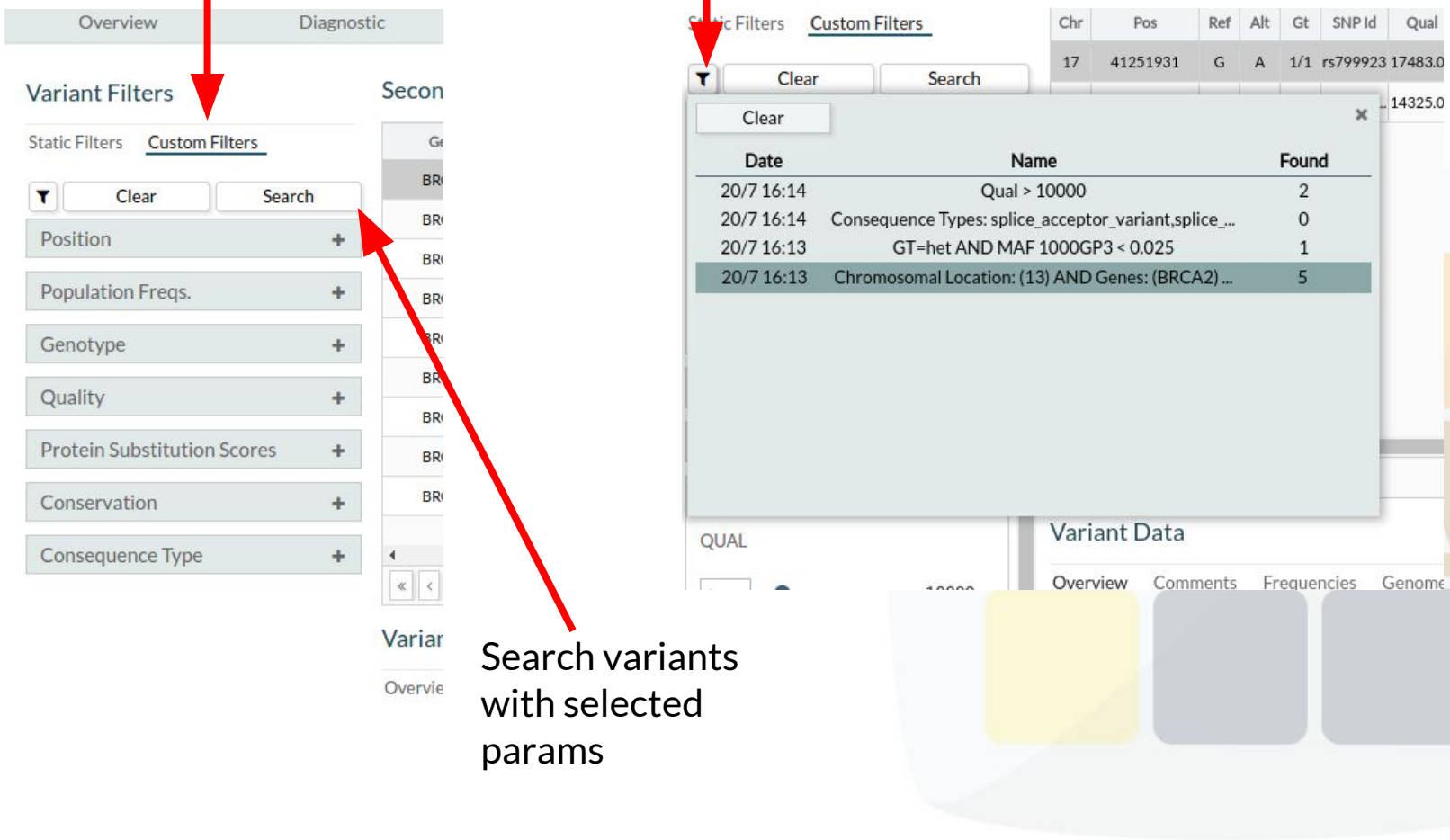
We have static filters for categorize Secondary findings variants in four levels.

We also found 4 variants within the genes defined in our panel.
Maybe we can discover an interesting variant here.

Results: Secondary Findings

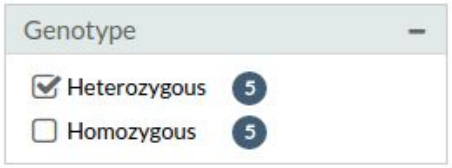
Custom filters

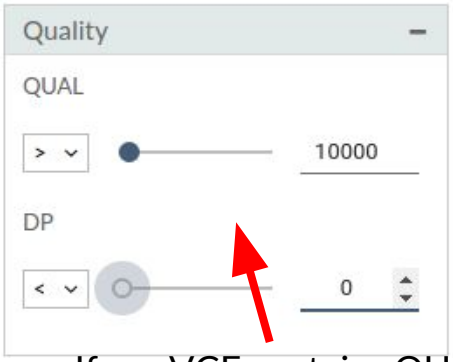
You can see filters used previously in Filters History



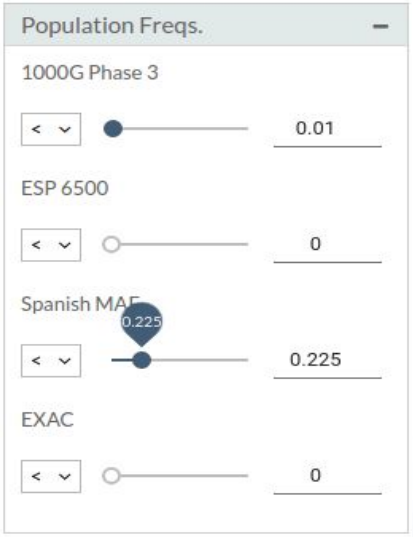
Search variants with selected params

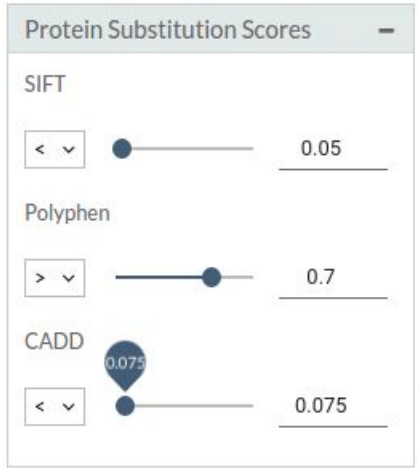
Results: Secondary Findings (Filters)

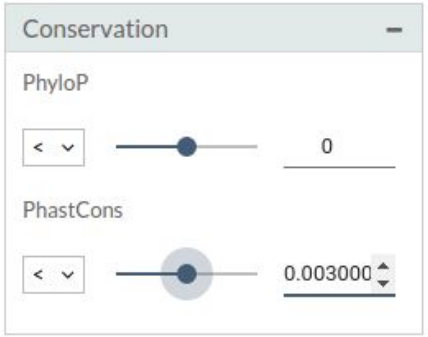


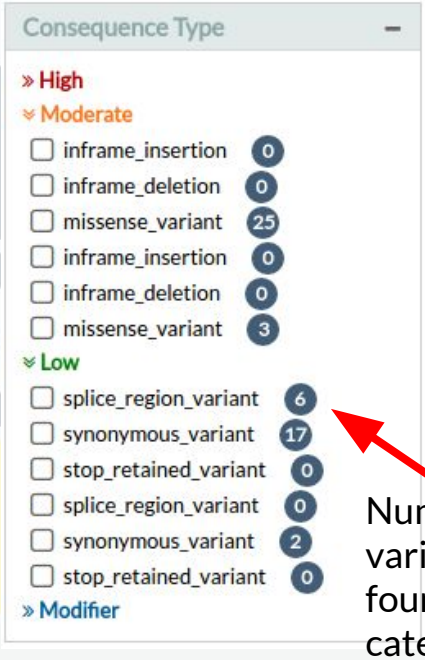


If our VCF contains QUAL & DP we can filter using them.









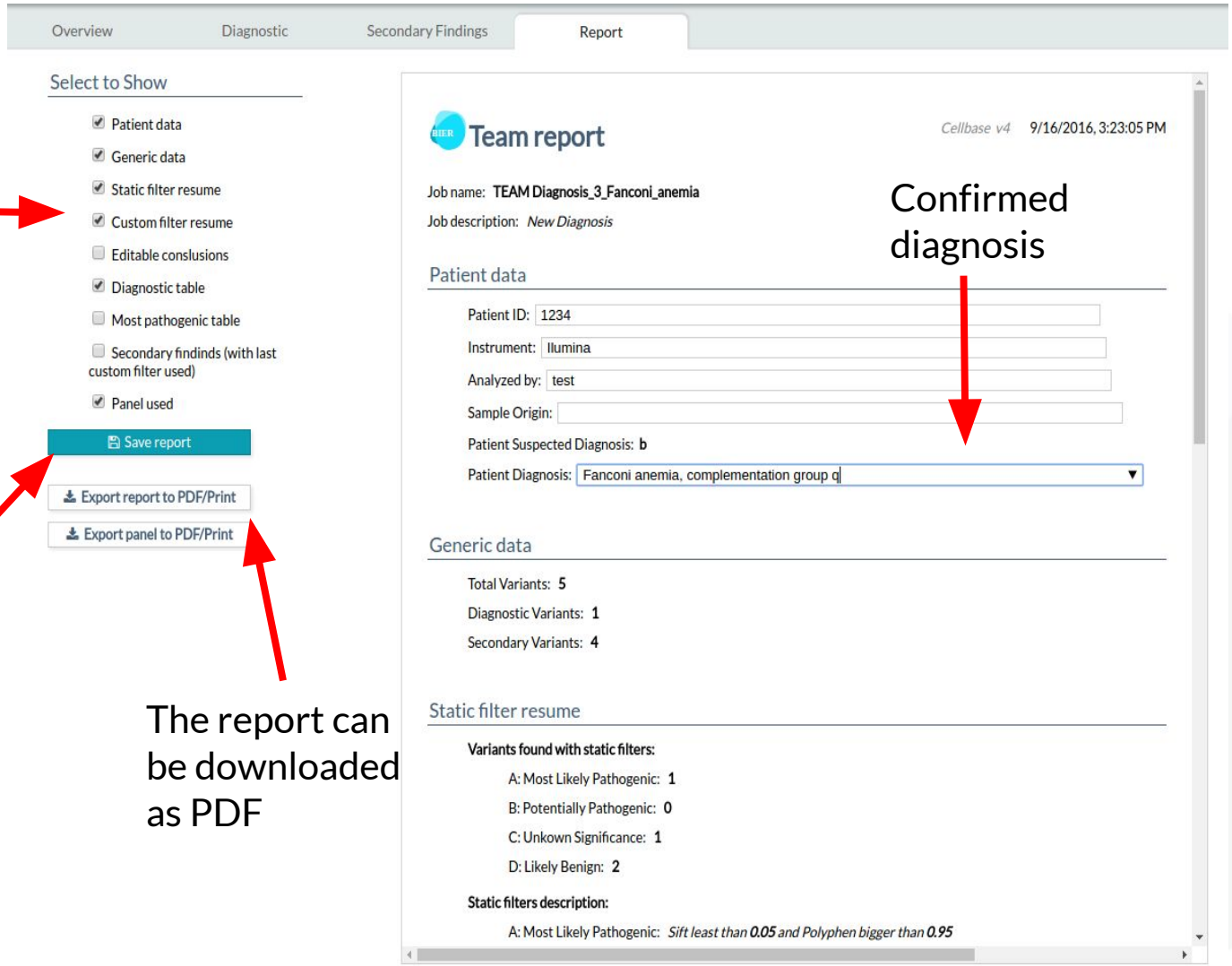
Number of variants found in each category

Results: Report

We can choose which sections we want to print

Complete the information about patient and save the report for a next view

The report can be downloaded as PDF



Who is using TEAM?

ciberer isciii | Centro de Investigación Biomédica en Red Enfermedades Raras

IT4Innovations
national!$11€0
supercomputing
center1001$1$0

Conclusions

- TEAM is a **free and easy-to-use web tool** that fills the gap between the enormous amount of data in targeted enrichment sequencing analysis and the **biological knowledge** available.

- TEAM **provides an intuitive environment for the clinicians** in which unprocessed data on patient's genomic variation can easily be transformed in a **diagnostic**.

- All data is stored in a Server so you can access to you diagnostics in anywhere you want.

More info: publication

Nucleic Acids Research Advance Access published May 26, 2014

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doi: 10.1093/nar/gku472

A web tool for the design and management of panels of genes for targeted enrichment and massive sequencing for clinical applications

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More info: TEAM behind the scenes