

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

Álex Alemán

March 2nd, 2016



GDA

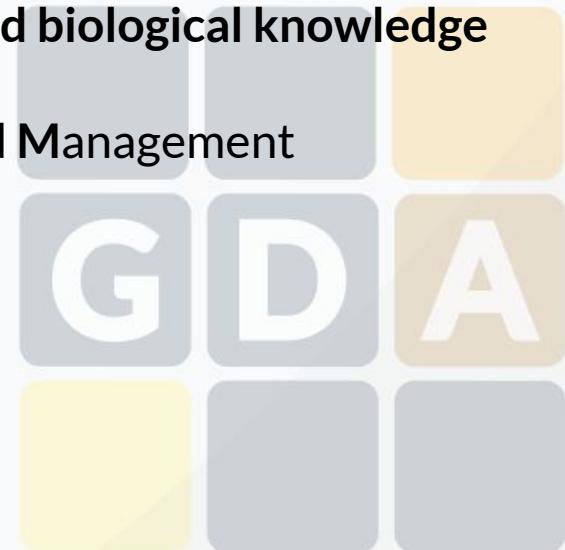
International Course on
Genomic Data Analysis



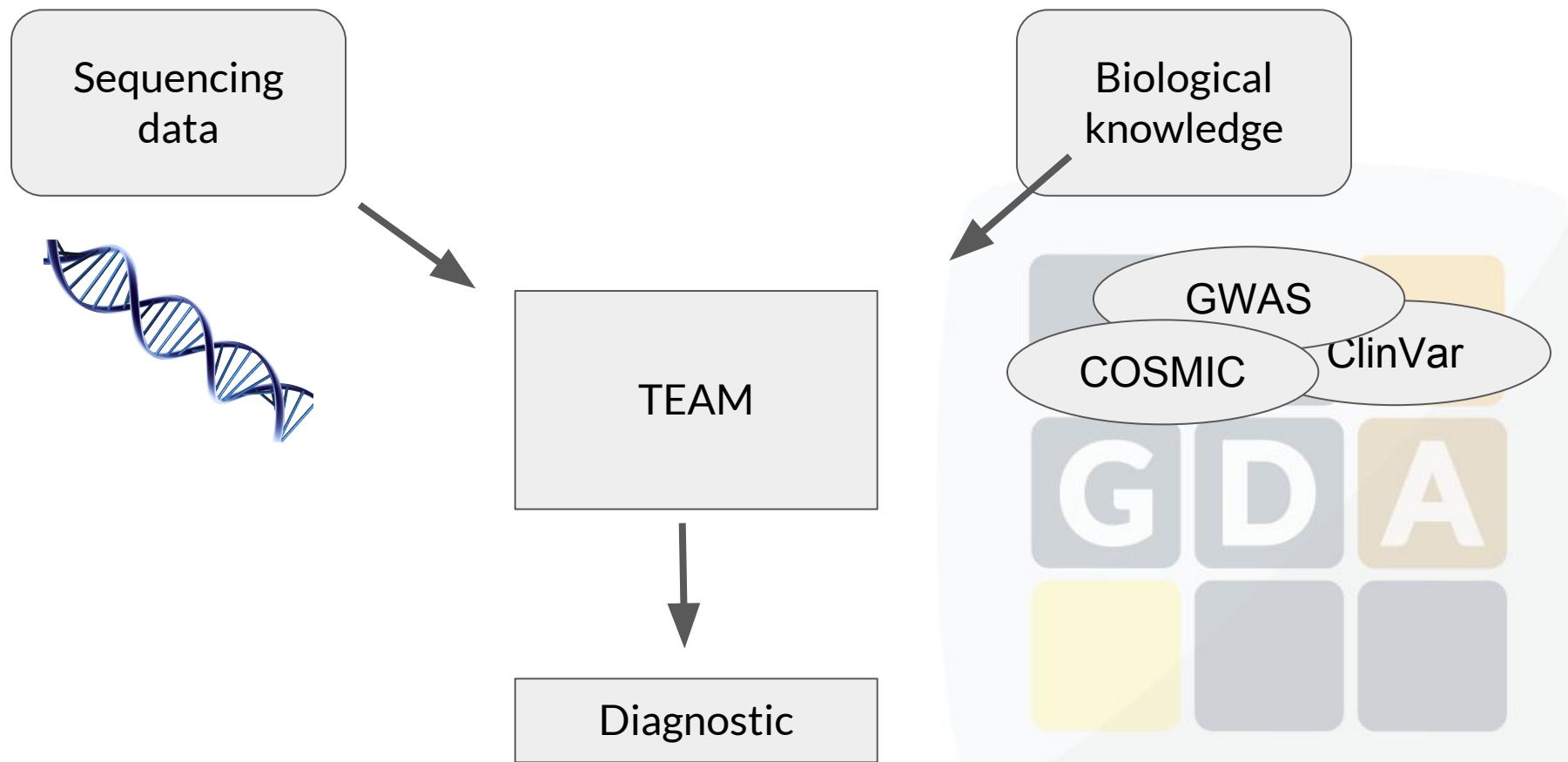
PRINCIPE FELIPE
CENTRO DE INVESTIGACION

Introduction

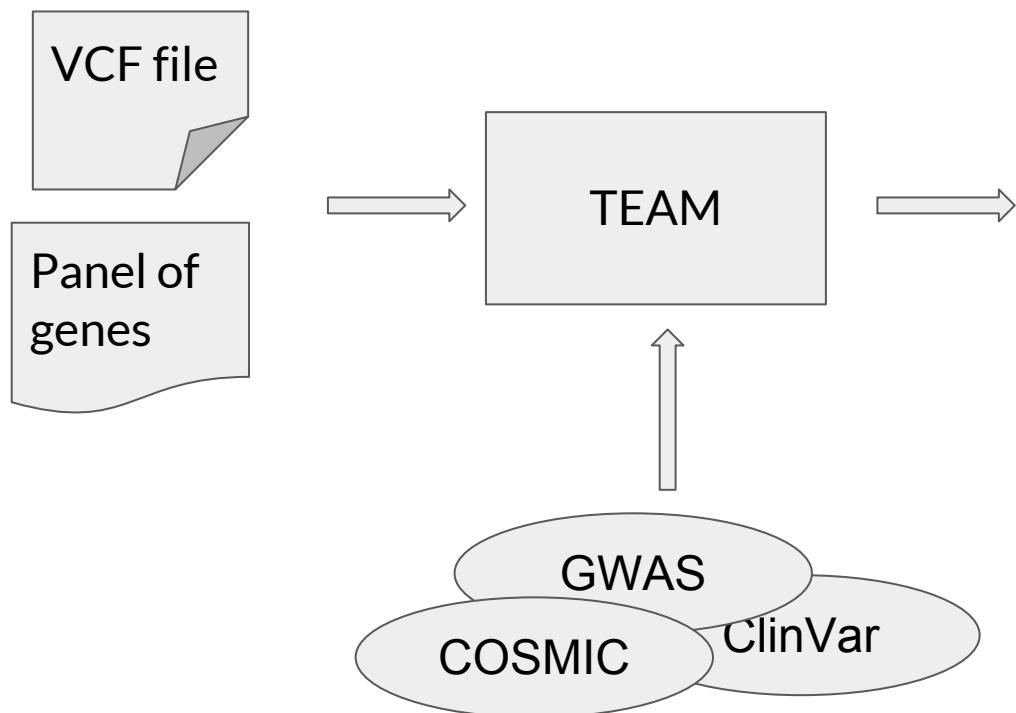
- ❑ **Development of high throughput sequencing technologies:**
 - ❑ Fast and economical genome sequencing
 - ❑ Disease targeted sequencing: powerful and cost-effective application
- ❑ **Vast amount of biological knowledge available:**
 - ❑ HGMD-public, HUMSAVAR, ClinVar, COSMIC
- ❑ We need a tool to connect **sequencing data and biological knowledge for diagnostic:**
 - ❑ TEAM (Targeted Enrichment Analysis and Management



Introduction



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

ClinVar

ClinVar aggregates information about genomic variation and its relationship to human health.



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/>



SIFT

- **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 (benign)

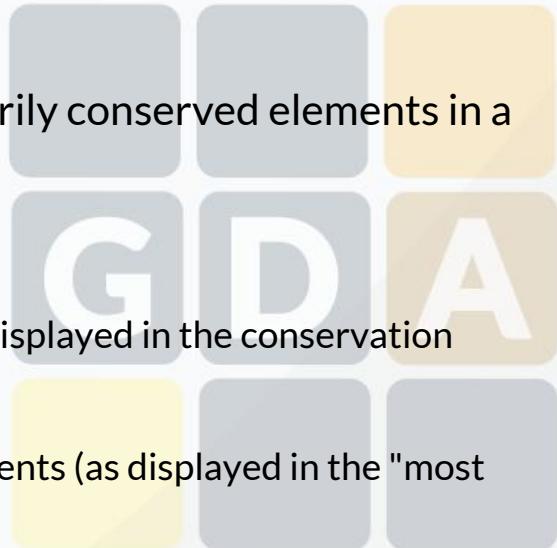
<http://genetics.bwh.harvard.edu/pph2/index.shtml>



PolyPhen-

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

e!Ensembl BLAST/BLAT | BioMart | Tools | Downloads | Help & Documentation | Blog | Mirrors

Using this website Annotation and prediction Data access API & software About us

In this section

- Web interface
 - Input form
 - Results
- VEP script
 - Tutorial
 - Download and install
 - Running the script
 - Caches and databases
 - Filtering results
 - Custom annotations
 - Plugins
 - Examples and use cases
 - Other information
- Data formats
- FAQ

Search documentation...

Help & Documentation > API & Software > Ensembl Tools > Variant Effect Predictor

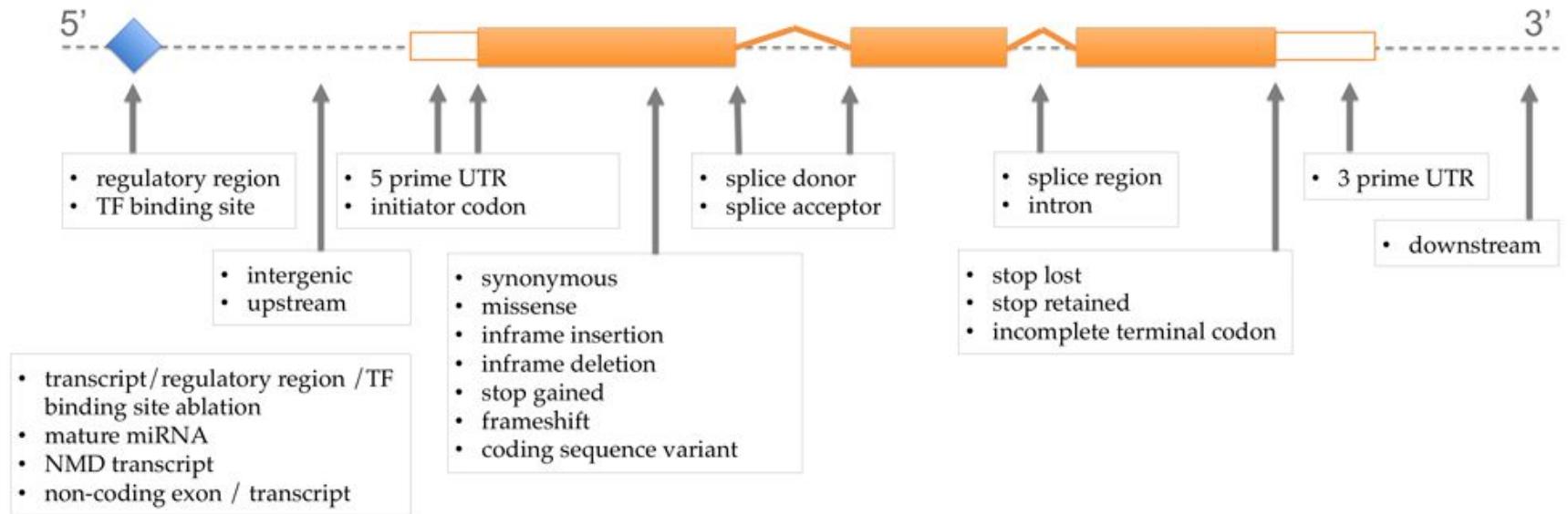
Variant Effect Predictor

The VEP determines the effect of your variants (SNPs, insertions, deletions, CNVs or structural variants) on genes, transcripts, and protein sequence, as well as regulatory regions. Simply input the coordinates of your variants and the nucleotide changes to find out the:

- **genes and transcripts** affected by the variants
- **location** of the variants (e.g. upstream of a transcript, in coding sequence, in non-coding RNA, in regulatory regions)
- **consequence** of your variants on the protein sequence (e.g. stop gained, missense, stop lost, frameshift)
- **known variants** that match yours, and associated minor allele frequencies from the **1000 Genomes Project**
- **SIFT and PolyPhen** scores for changes to protein sequence
- ... And [more!](#)

A large blue button with a white play icon on the left and the text "Launch Ve!P" on the right. The "Ve!P" part is in a stylized font.

Getting information: Effect



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



Inputs: Panel + VCF

1. TEAM needs a Panel of genes and a VCF file:
 - a. The VCF file needs to be stored/indexed in our database.
 - b. This file could be already added if we used BiERapp (both tools are compatible)
2. What is a Panel of genes:.
 - a. TEAM works with virtual panel of genes.
 - b. You can design/create/manage these panels using TEAM.
 - c. These panels contains:
 - i. Phenotypes
 - ii. Genes
 - iii. Mutations



Tool interface: Official release

<http://team.babelomics.org/>

TEAM

Example Data

Search

Panel: Select a Panel... VCF File: Select a file Browse... Run Reset

Results

Diagnostic Secondary findings

Chromosome	Position	SNP Id	Ref	Alt	Gene	Conseq. Type	Phenotype	Source	SIFT	PolyPhen	Conservation
------------	----------	--------	-----	-----	------	--------------	-----------	--------	------	----------	--------------

Generate Report

Variant Effect

Position chr:start:end (strand)	SNP Id	Conseq. Type	Aminoacid Change	Gene (Ensembl)	Transcript Id	Feature Id	Feature Name	Feature Type	Feature Biotype
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Tool interface: Beta

<http://team.babelomics.org/beta>

The screenshot shows the TEAM (Targeted Enrichment Analysis and Management) web application. At the top left is the BIER logo (a blue circle with white text). To its right is the word "TEAM" in white. On the far right are "Login" and "Sign up" buttons. Below the header, there's a large teal circular graphic containing the word "BIER". To the right of this graphic, the word "TEAM" is written again in a large, light-colored font. Below these elements is the section title "Overview". A paragraph describes TEAM as an open web-based tool for gene panel design and management. Below the paragraph is the heading "Supported by" followed by several logos of supporting organizations. At the bottom, there's a "Note:" section with a note about browser compatibility. The footer contains copyright information: "TEAM: created by Computational Genomics Department Centro de Investigación Príncipe Felipe 2015".

TEAM 1.1.0

BIER

TEAM

Overview

TEAM (Targeted Enrichment Analysis and Management) is an open web-based tool for the design and management of panels of genes for targeted enrichment and massive sequencing for diagnostic applications.

Supported by

ciberer BIMB er ciberer PRINCIPE FELIPE CENTRO DE INVESTIGACIONES INB

Note:

TEAM web application makes an intensive use of the HTML5 standard and other cutting-edge web technologies such as Web Components, so only modern web browsers are fully supported, these include Chrome 36+, Firefox 32+, IE 10+, Safari 7+ and Opera 24+.

TEAM: created by Computational Genomics Department
Centro de Investigación Príncipe Felipe
2015

Tool interface: Beta

Design/Manage Panels

Data & Diagnoses

The screenshot shows the TEAM web application interface. At the top, there is a dark blue header bar with the TEAM logo on the left and a search bar on the right. Below the header is a navigation bar with several items: '+ Diagnosis', '+ Panel', and 'Panels' on the left, and 'My data', 'Samples', and 'Diagnoses' on the right. Both the 'Panels' and 'Diagnoses' sections are highlighted with red boxes and arrows pointing to them from the text above. The main content area has a teal background with a large blue circle containing the text 'BIER'. The word 'TEAM' is written in large white letters to the right of the circle. Below this, the word 'Overview' is centered. A paragraph of text follows, describing TEAM as an open web-based tool for gene panel design and management. The 'Supported by' section contains logos of various organizations, including ciberER, PRINCIPE FELIPE, and others. A 'Note:' section at the bottom provides information about browser compatibility.

TEAM 1.1.0

+ Diagnosis + Panel Panels

My data Samples Diagnoses

test profile logout ?

BIER

TEAM

Overview

TEAM (Targeted Enrichment Analysis and Management) is an open web-based tool for the design and management of panels of genes for targeted enrichment and massive sequencing for diagnostic applications.

Supported by

ciberER er ciberer PRINCIPE FELIPE INSTITUTO NACIONAL DE CIENCIAS Y TECNOLOGÍAS

Note:

TEAM web application makes an intensive use of the HTML5 standard and other cutting-edge web technologies such as Web Components, so only modern web browsers are fully supported, these include Chrome 36+, Firefox 32+, IE 10+, Safari 7+ and Opera 24+.

TEAM: created by Computational Genomics Department
Centro de Investigación Príncipe Felipe
2015

Panel Designer

Select
“+ Panel”

The screenshot shows the 'Panel Designer' software interface. At the top left, there are two buttons: '+ Diagnosis' and '+ Panel'. The '+ Panel' button is highlighted with a red box and a red arrow pointing to it from the text 'Select “+ Panel”' on the left. The top navigation bar includes 'Panels', 'My data', 'Samples', and 'Diagnoses'. The main window is titled '+ New Panel' and 'Step 1: Select Diseases'. It displays a table of phenotypes and sources, with a total of 14923 items. The table has columns for 'Phenotype' and 'Source'. The 'Source' column for most items is 'clinvar'. The bottom right of the main window has a 'Clear' button and a 'Next »' button. The status bar at the bottom right shows 'Total: 0'.

Phenotype	Source
filter by Phenotype	
Asthma, susceptibility to	clinvar
Deficiency of acetyl-CoA acetyltransferase	clinvar
Familial Hypercholesterolemia, Autosomal Dominant, 3	clinvar
Mitochondrial Disorders (Leigh syndrome/Mitochondrial Myopat...	clinvar
Myoclonus with epilepsy with ragged red fibers	clinvar
Peroxisome Biogenesis Disorders, Zellweger Syndrome Spectrum	clinvar
'antithrombin' pittsburgh	clinvar
β2-Glycoprotein I (β2-GPI) plasma levels	gwas
•Autosomal recessive polycystic kidney disease	clinvar
11-alpha beta-hydroxylase deficiency	clinvar
11-alpha beta-hydroxysteroid dehydrogenase type I deficiency of	clinvar
11-beta-hydroxylase deficiency	clinvar
17 beta-hydroxysteroid dehydrogenase type 10 deficiency	clinvar
17q21.31 deletion syndrome	clinvar
17q21.31 microdeletion syndrome	clinvar

Panel Designer: Diseases

Write the phenotypes you are interested in.

New Panel

Step 1 : Select Diseases

Step 2

Phenotype

Asthma, susceptibility to
Deficiency of acetyl-CoA acetyltransferase
Familial Hypercholesterolemia, Autosomal Dominant, 3
Mitochondrial Disorders (Leigh syndrome/Mitochondrial Myopat...
Myoclonus with epilepsy with ragged red fibers
Peroxisome Biogenesis Disorders, Zellweger Syndrome Spectrum
'antithrombin' pittsburgh
 β 2-Glycoprotein I (β 2-GPI) plasma levels
•Autosomal recessive polycystic kidney disease
11-alpha beta-hydroxylase deficiency
11-alpha beta-hydroxysteroid dehydrogenase type I deficiency of
11-beta-hydroxylase deficiency
17 beta-hydroxysteroid dehydrogenase type 10 deficiency
17q21.31 deletion syndrome
17q21.31 microdeletion syndrome

Total: 0

Next »

Clear

Add

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Panel Designer: Diseases

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

Step 1 : Select Diseases Step 2 ►

Phenotype	Source
retinitis	clinvar
AIPL1-Related Retinitis Pigmentosa	clinvar
Ataxia and retinitis pigmentosa with isolated vitamin e deficiency	clinvar
Fundus albipunctatus, RETINITIS PUNCTATA ALBESCENS, PERI...	clinvar
Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentos...	clinvar
Juvenile retinitis pigmentosa, AIPL1-related	clinvar
MICROPHTHALMIA, POSTERIOR, WITH RETINITIS PIGMENTO...	clinvar
Neuropathy ataxia retinitis pigmentosa syndrome	clinvar
Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cat...	clinvar
Posterior column ataxia with retinitis pigmentosa	clinvar
Retinitis pigmentosa	clinvar
Retinitis pigmentosa 1	clinvar
Retinitis pigmentosa 10	clinvar
Retinitis pigmentosa 11	clinvar
Retinitis pigmentosa 12	clinvar
Retinitis pigmentosa 13	clinvar

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Add

Step 2 ►

Phenotype	Source
Loading...	

Total: 0

Clear

Next »

Click
“Add”

Panel Designer: Diseases

+ New Panel

Step 1 : Select Diseases

Step 2 ►►

Phenotype	Source	
retinitis	clinvar	X
AIPL1-Related Retinitis Pigmentosa	clinvar	
Ataxia and retinitis pigmentosa with isolated vitamin e deficiency	clinvar	
Fundus albipunctatus , RETINITIS PUNCTATA ALBESCENS, PERI...	clinvar	
Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentos...	clinvar	
Juvenile retinitis pigmentosa, AIPL1-related	clinvar	
MICROPHTHALMIA, POSTERIOR, WITH RETINITIS PIGMENTO...	clinvar	
Neuropathy ataxia retinitis pigmentosa syndrome	clinvar	
Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cat...	clinvar	
Posterior column ataxia with retinitis pigmentosa	clinvar	
Retinitis pigmentosa	clinvar	
Retinitis pigmentosa 1	clinvar	
Retinitis pigmentosa 10	clinvar	
Retinitis pigmentosa 11	clinvar	
Retinitis pigmentosa 12	clinvar	
Retinitis pigmentosa 13	clinvar	

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Add

Phenotype	Source	
Retinitis pigmentosa 1	clinvar	X
Retinitis pigmentosa 10	clinvar	X
Retinitis pigmentosa 11	clinvar	X
Retinitis pigmentosa 12	clinvar	X
Retinitis pigmentosa 13	clinvar	X
Retinitis pigmentosa	clinvar	X

Total: 6

Clear

Next »

Panel Designer: Genes

Selected Diseases in previous step.

These genes have been added by previous step.

These genes are related to the selected diseases

Step 1

Diseases Selected:

- Retinitis pigmentosa 1
- Retinitis pigmentosa 10
- Retinitis pigmentosa 11
- Retinitis pigmentosa 12
- Retinitis pigmentosa 13
- Retinitis pigmentosa

Step 2 : Select Genes

Step 3

Name	Chr	Start	End	X
RP1	8	55528627	55543394	X
IMPDH1	7	128032331	128050306	X
PRPF31	19	54618837	54635140	X
CRB1	1	197170592	197447585	X
PRPF8	17	1553923	1588176	X
RP1L1	8	10463859	10569697	X
ZFYVE26	14	68194091	68283307	X
SNRNP200	2	96940074	96971297	X
PRPF6		.	.	X
MERTK	2	112656056	112787138	X
C2orf71	2	29283842	29297127	X
MYO7A	11	76839310	76926284	X
MAK	6	10762956	10838764	X
NR2E3	15	72084977	72110600	X
CRX	19	48322703	48346587	X
RPE65	1	68894505	68915642	X
TOPORS	9	32540542	32552551	X

Total: 35

Add Genes

Import from BED

Import

Import from other Panel

View Panel Import

Import from external App

Panel App Import

Clear

« Previous Next »

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.

Other way is using PanelApp tool

The screenshot shows the 'Genes/Regions' section of the Panel Designer. On the left, there are four import methods:

- Genes/Regions:** A text input field containing 'BRCA2, PPL' with a red arrow pointing to it.
- Import from BED:** A button labeled 'Import' with a red arrow pointing to it.
- Import from other Panel:** A dropdown menu with 'Review Panel' selected, followed by a 'Import' button.
- Import from external App:** A radio button labeled 'Panel App' selected, followed by an 'Import' button.

To the right is a table listing gene regions:

Name	Chr	Start	End	X
RP1	8	55528627	55543394	X
IMPDH1	7	128032331	128050306	X
PRPF31	19	54618837	54635140	X
CRB1	1	197170592	197447585	X
PRPF8	17	1553923	1588176	X
RP1L1	8	10463859	10569697	X
ZFYVE26	14	68194091	68283307	X
SNRNP200	2	96940074	96971297	X
PRPF6	.	.	.	X
MERTK	2	112656056	112787138	X
C2orf71	2	29283842	29297127	X
MYO7A	11	76839310	76926284	X
MAK	6	10762956	10838764	X
NR2E3	15	72084977	72110600	X
CRX	19	48322703	48346587	X
RPE65	1	68894505	68915642	X
TOPORS	9	32540542	32552551	X

Total: 35

Clear

Panel Designer: Genes (PanelApp)

Import From PanelApp

Disease	NºGenes	Version
conge	filter by NºGenes	filter by Version
Congenital myaesthesia	17	0.0
Congenital myopathy	64	0.0
Leber Congenital Amaurosis / Early-Onset S...	30	0.0
Congenital adrenal hypoplasia	18	0.10
Congenital hearing impairment (profound/s...	348	0.382
Congenital neutropaenia	15	0.20
Paediatric congenital malformation-dysmor...	39	0.38
Congenital muscular dystrophy	38	0.0
Congenital anaemias	83	0.94
Autosomal recessive congenital ichthyosis	12	0.3

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>>More info <<

Gene	Level Of Confidence
CHAT	HighEvidence
CHRNA1	HighEvidence
CHRNB1	HighEvidence
CHRNQ	HighEvidence
CHRNE	HighEvidence
DOK7	HighEvidence
GFPT1	HighEvidence
MUSK	HighEvidence
RAPSN	HighEvidence
SCN4A	HighEvidence
COLQ	ModerateEvidence
DPAGT1	ModerateEvidence
AGRN	LowEvidence
ALG2	LowEvidence
CHRNQ	LowEvidence
GRN	LowEvidence
SYT2	LowEvidence

Total: 17

Add Genes

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

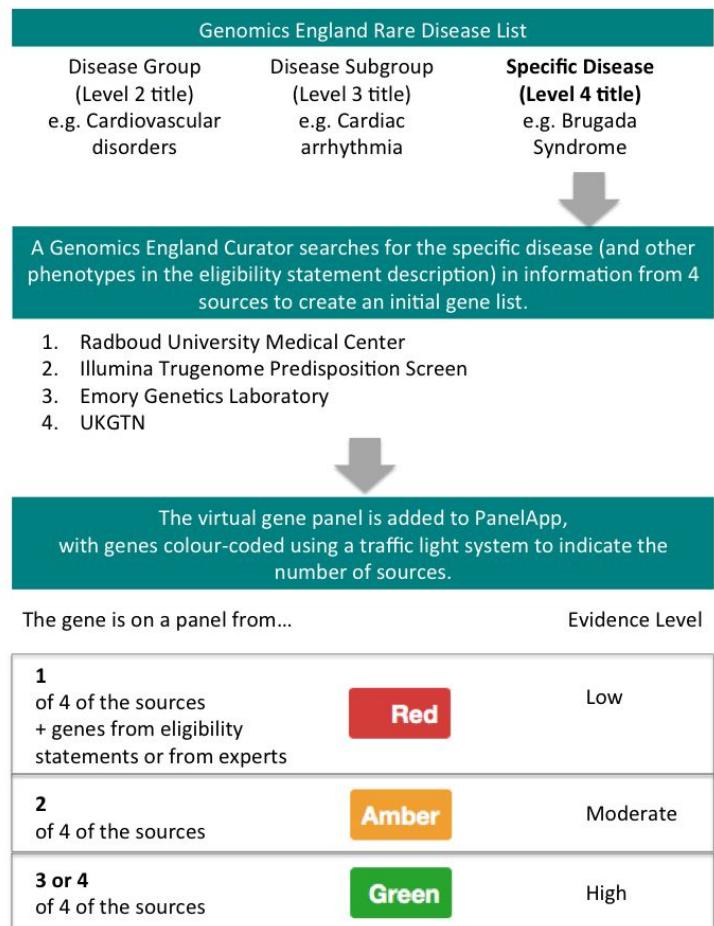
High, diagnostic-grade gene that will be used to Interpret genomes.

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

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

The screenshot shows the 'Panel Designer: Mutations' interface. On the left, there are four input sections: 'Genomic Pos.' (Chr: [] Pos: [], Ref: [] Alt: [], Phe: [], Open Genome Browser, + Add), 'Import VCF' (Phe: [], + Import), 'Import CSV' (Separator: [;], Ignore first line (header): [checked], Choose File [No file chosen], + Import), and 'Import from other Panel' (dropdown menu, View Panel, + Import). On the right, a table lists mutations with columns: Chr, Pos, Ref, Alt, Phenotype, Source, and a delete icon. A red arrow points to the row for mutation 54633399, which has Chr: 19, Pos: 54633399, Ref: C, Alt: T, Phenotype: Retinitis pigmentosa 1, and Source: clinvar.

Chr	Pos	Ref	Alt	Phenotype	Source	
17	1554178	T	C	Retinitis pigmentosa 1	clinvar	x
17	1554178	T	G	Retinitis pigmentosa 1	clinvar	x
17	1554175	C	T	Retinitis pigmentosa 1	clinvar	x
17	1554203	G	T	Retinitis pigmentosa 1	clinvar	x
17	1554192	G	C	Retinitis pigmentosa 1	clinvar	x
19	54627246	G	C	Retinitis pigmentosa 1	clinvar	x
19	54626942	A	G	Retinitis pigmentosa 1	clinvar	x
19	54627181	C	A	Retinitis pigmentosa 1	clinvar	x
19	54633399	C	T	Retinitis pigmentosa 1	clinvar	x
1	19740411	T	C	Retinitis pigmentosa 1	clinvar	x
1	19740397	G	T	Retinitis pigmentosa 1	clinvar	x
1	19739674	C	T	Retinitis pigmentosa 1	clinvar	x
1	19739668	C	T	Retinitis pigmentosa 1	clinvar	x
1	19739685	A	T	Retinitis pigmentosa 1	clinvar	x
1	19740453	T	C	Retinitis pigmentosa 1	clinvar	x
1	19740430	G	A	Retinitis pigmentosa 1	clinvar	x
8	55538477	C	T	Retinitis pigmentosa 1	clinvar	x

Total: 481 Clear

Panel Designer: Mutations

Genomic Pos.

Chr: Pos:

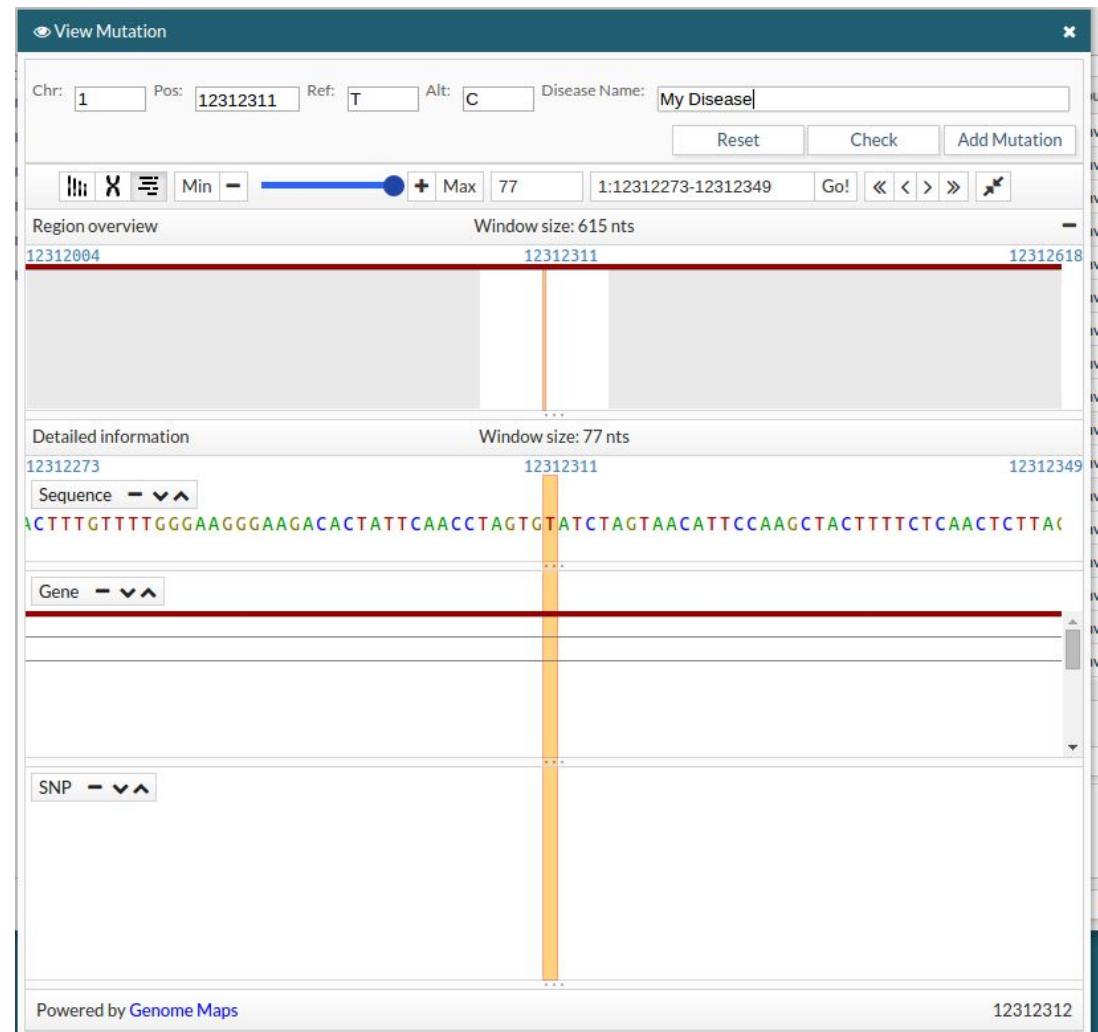
Ref: Alt:

Phe:

[Open Genome Browser](#) [Add](#)

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



Panel Designer: Mutations

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

Importing mutations from other virtual panels is supported too.

Genomic Pos.

Chr: [] Pos: []

Ref: [] Alt: []

Phe: []

Import VCF

Phe: []

Import CSV

Separator: [,]

Ignore first line (header):

No file chosen

Import from other Panel

Chr	Pos	Ref	Alt	Phenotype	Source	X
17	1554178	T	C	Retinitis pigmentosa 1	clinvar	X
17	1554178	T	G	Retinitis pigmentosa 1	clinvar	X
17	1554175	C	T	Retinitis pigmentosa 1	clinvar	X
17	1554203	G	T	Retinitis pigmentosa 1	clinvar	X
17	1554192	G	C	Retinitis pigmentosa 1	clinvar	X
19	54627246	G	C	Retinitis pigmentosa 1	clinvar	X
19	54626942	A	G	Retinitis pigmentosa 1	clinvar	X
19	54627181	C	A	Retinitis pigmentosa 1	clinvar	X
19	54633399	C	G	Retinitis pigmentosa 1	clinvar	X
1	19740411	T	C	Retinitis pigmentosa 1	clinvar	X
1	19740397	G	T	Retinitis pigmentosa 1	clinvar	X
1	19739674	C	T	Retinitis pigmentosa 1	clinvar	X
1	19739668	C	T	Retinitis pigmentosa 1	clinvar	X
1	19739685	A	T	Retinitis pigmentosa 1	clinvar	X
1	19740453	T	C	Retinitis pigmentosa 1	clinvar	X
1	19740430	G	A	Retinitis pigmentosa 1	clinvar	X
8	55538477	C	T	Retinitis pigmentosa 1	clinvar	X

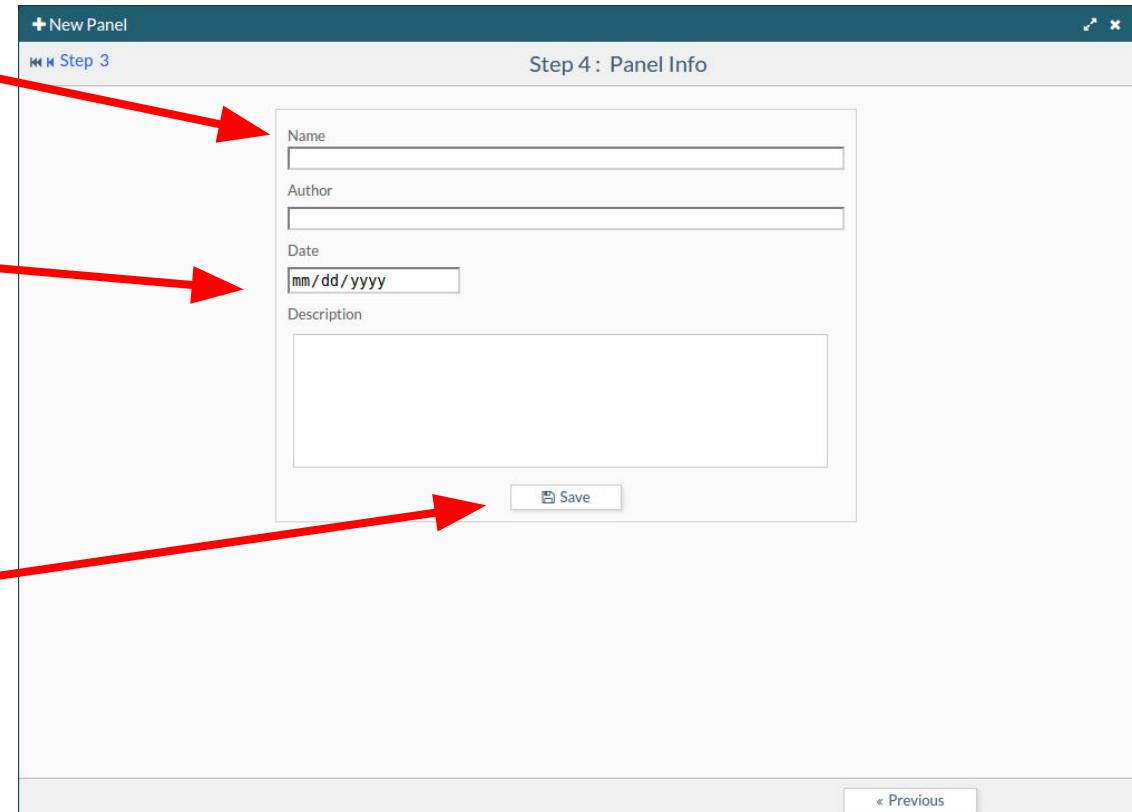
Total: 481

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



Panel Manager

You can manage your panels using “Panels”

The screenshot shows the 'Panel Manager' interface. At the top, there is a navigation bar with the following items: 'TEAM 1.10', '+ Diagnosis', '+ Panel', a 'Panels' button (which is highlighted with a red box and has a red arrow pointing to it), 'My data', 'Samples', 'Diagnoses', and user account information ('test', 'profile', 'logout'). Below the navigation bar is the main content area. On the left, there is a sidebar titled 'Panel Manager' containing two sections: 'User Panel List' (with tabs for 'Main Panels' and 'Archived Panels') and 'Example Panel List'. The 'User Panel List' section shows four panels: 'retinitis_test', 'panelTest', 'asthma', and 'cardiac'. The 'Example Panel List' section shows one panel: 'retinitis'. At the bottom of the sidebar is a button 'Or create a New Panel' with a '+ Panel' icon. The main content area on the right is titled 'Panel Preview' and contains fields for 'Name', 'Author', and 'Version', along with a table for 'Panel Content' with columns for 'Diseases', 'Genes/Regions', and 'Mutations'. A message at the bottom of the preview area says 'Total: 0'.

New Diagnosis

Click “+ Diagnosis”

Choose a Study.
And then a
patient/sample

The screenshot shows the BIER software interface for creating a new diagnosis. At the top, there is a navigation bar with a logo, team name 'TEAM 110', and various menu items like '+ Diagnosis', '+ Panel', 'Panels', 'My data', 'Samples', 'Diagnoses', and user profile information. A red arrow points from the text 'Click “+ Diagnosis”' to the '+ Diagnosis' button in the top navigation bar. Another red arrow points from the text 'Choose a Study. And then a patient/sample' to the study selection area. In the main window, titled '+ New Diagnosis', the user is prompted to 'Step 1: Choose a Sample'. On the left, a sidebar shows a hierarchy of projects and studies: 'Default project' (with 'Default study'), 'family' (with 'fam1', 'fam2', 'fam3'), and 'family2' (with 'fam2'). On the right, a table lists samples with columns for Name, Status, and Source. The sample 'HG01501' is selected, indicated by a grey background. A red arrow points to this selected sample. The table data is as follows:

	Name	Status	Source
Default project	HG01500	✓ READY	HG01500_HG0150...
Default study	HG01501	✓ READY	HG01500_HG0150...
family	HG01501_HG0...	✓ READY	HG01500_HG0150...
fam1	HG01500_HG0...	✓ READY	HG01500_HG0150...
fam2	HG01500_HG0...	✓ READY	HG01500_HG0150...
family2	HG01500_HG0...	✓ READY	HG01500_HG0150...
fam2	HG01500_HG0...	✓ READY	HG01500_HG0150...
family3	HG01500_HG0...	✓ READY	HG01500_HG0150...
fam3			

At the bottom of the main window, it says 'Study Type: FAMILY'. A red arrow points from the text 'Next Step' to the 'Next >' button at the bottom right.

New Diagnosis

Select the panel to be used.

The screenshot shows the 'New Diagnosis' application interface. On the left, there's a sidebar with 'Step 1' and 'Step 3'. The main area is titled 'Step 2: Choose a Panel' and contains a 'Panel Preview' section. In the preview, a panel named 'cardiac' is selected, as indicated by a red arrow pointing to its name in the 'User Panel List'. The preview shows the panel's details: Name: cardiac, Author: (empty), Version: 1. It also lists diseases, genes/regions, and mutations associated with the phenotype. Below the preview, there's an 'Example Panel List' containing 'retinitis' and a button to 'Or create a New Panel'. A red arrow points from the text 'Select the panel to be used.' to the 'cardiac' panel in the list. Another red arrow points from the text 'Next Step' to the 'Next >' button at the bottom right of the screen.

Step 2 : Choose a Panel

User Panel List

retinitis_test
panelTest
rhma
cardiac

Panel Preview

Name: **cardiac** Author: Version: 1

Description:

Diseases	Genes/Regions	Mutations
Phenotype		Source
Cardiac arrhythmia		clinvar
Cardiac arrhythmias		clinvar
Cardiac conduction defect, nonprogressive		clinvar
CARDIAC CONDUCTION DEFECT, NONSPECIFIC		clinvar

Example Panel List

retinitis

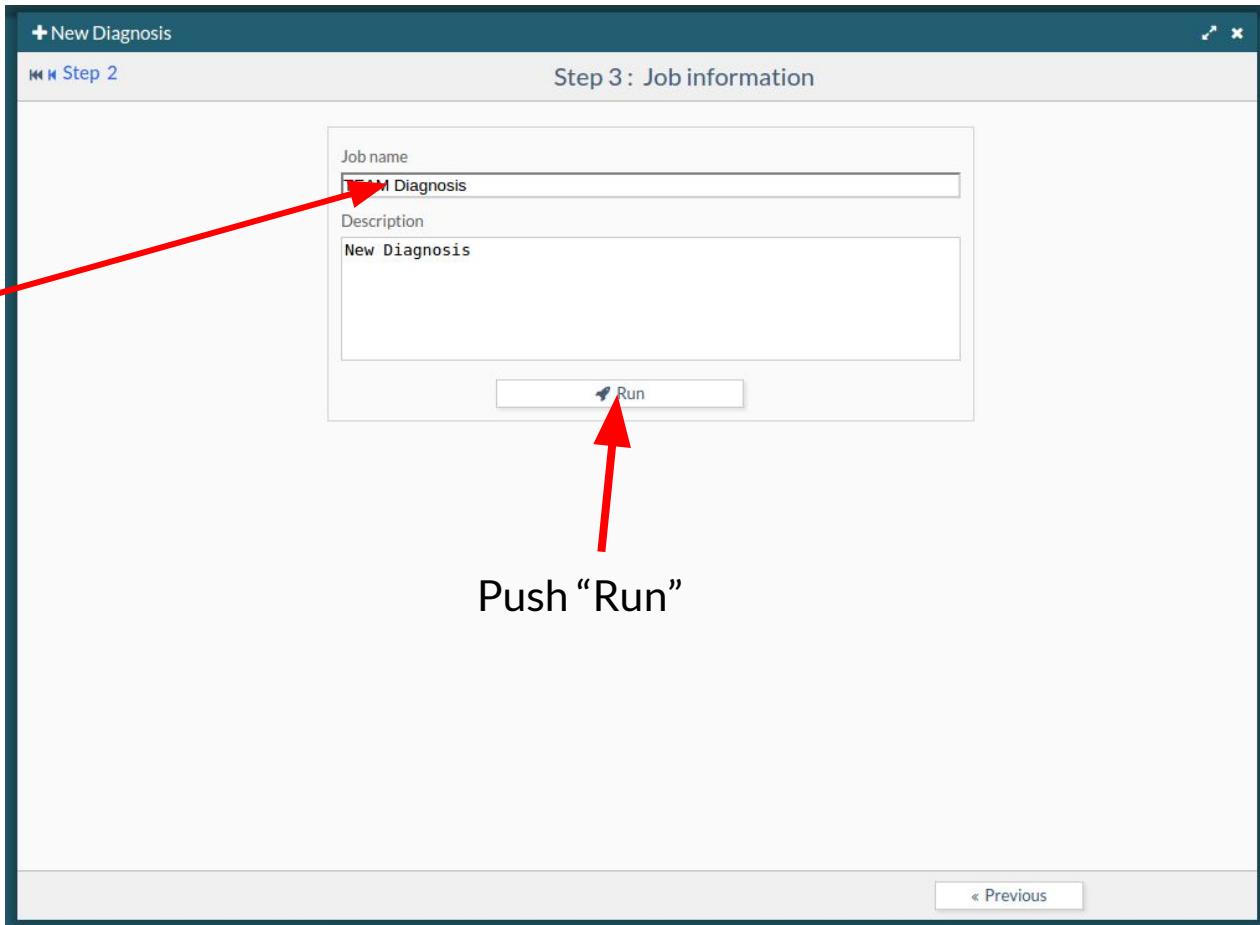
Or create a New Panel **+ Panel**

Total: 4

« Previous **Next >**

New Diagnosis

Give a name
to the new
diagnosis/job



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.

The screenshot shows a software application window titled 'Diagnoses'. At the top, there is a navigation bar with links for 'My data', 'Samples', 'Diagnoses' (which is highlighted with a red box and arrow), 'test', 'profile', 'logout', and a help icon. Below the navigation bar is a sidebar titled 'Diagnoses Browser' containing a tree view of project and family structures:

- Default project
 - Default study
- family
 - fam1
- family2
 - fam2
- family3
 - fam3

To the right of the sidebar is a main panel titled 'Diagnoses Browser' showing a list of diagnosis entries. Each entry includes a status indicator (green circle for Running, blue checkmark for Ready, red X for Error), the diagnosis name ('TEAM Diagnosis' or 'panelTestMother'), the team name ('Team'), the status ('Running', 'Ready', or 'Error'), the date and time ('02/28/2016 19:17:55' or '02/26/2016 16:29:16'), and three action icons (trash, eye, info). A red arrow points from the text 'If you select a specific Diagnoses you will access to the results of that diagnoses.' to the 'Diagnoses' link in the top navigation bar. Another red arrow points from the text 'The different status are: QUEUED, RUNNING, READY, ERROR' to the 'Diagnoses' browser panel.

Status	Name	Team	Status	Date	Action
Green Circle	TEAM Diagnosis	Team	Running	02/28/2016 19:17:55	trash eye info
Blue Checkmark	TEAM Diagnosis	Team	Ready	02/26/2016 16:30:46	trash eye info
Blue Checkmark	TEAM Diagnosis	Team	Ready	02/26/2016 16:29:16	trash eye info
Blue Checkmark	TEAM Diagnosis	Team	Ready	02/26/2016 16:29:16	trash eye info
Blue Checkmark	TEAM Diagnosis	Team	Ready	02/26/2016 16:29:15	trash eye info
Blue Checkmark	panelTestMother	Team	Ready	02/26/2016 16:22:32	trash eye info
Red X	TEAM Diagnosis	Team	Error	02/26/2016 12:59:15	trash eye info
Red X	TEAM Diagnosis	Team	Error	02/26/2016 12:58:33	trash eye info
Red X	panelTestMother	Team	Error	02/26/2016 12:53:35	trash eye info
Red X	pather	Team	Error	02/26/2016 12:49:39	trash eye info
Red X	TEAM Diagnosis	Team	Error	02/26/2016 12:48:45	trash eye info

Results: Overview

Overview

Diagnostic

Secondary Findings

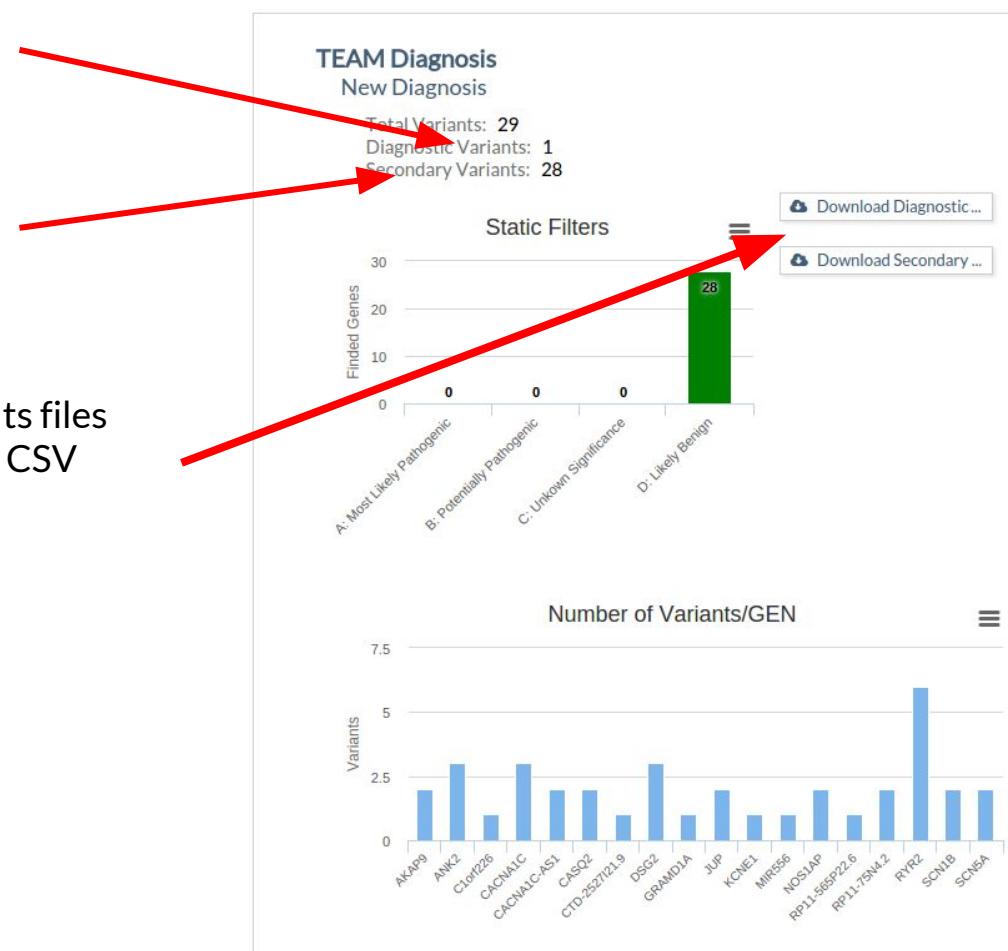
Report

We got one diagnostic variant

Secondary findings: 28

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: Diagnostic Variants

Overview Diagnostic Secondary Findings Report

Diagnostic

Chr	Pos	Ref	Alt	SNP Id	Qual	DP	Gene	Conseq. Type	phyloP	Phastcons	SIFT	Polyphen	MAF 1000G	MAF 1000G Phase...	ESP
4	114276880	T	C	rs28377576	.	.	ANK2	missense_variant,2KB_upstream_gene_variant,non_coding_tr...	-0.768	0.006	0.73	0	.	0.0921	0

« < Page 1 of 1 > » 1 - 1 of 1

We found a diagnostic variant

Overview Diagnostic Secondary Findings Report

Diagnostic

	phyloP	Phastcons	SIFT	Polyphen	MAF 1000G	MAF 1000G Phase...	ESP 6500 EA	ESP 6500 AA	Phenotype	Source
nt,non_coding_tr...	-0.768	0.006	0.73	0	.	0.0921	0.1163	0.1859	Cardiac arrhythmia	clinvar

« < Page 1 of 1 > » 1 - 1 of 1

iii Our variant appears in ClinVar!!!

Results: Secondary Findings

Overview Diagnostic Secondary Findings Report

Secondary Findings

Chr	Pos	Ref	Alt	SNP Id	Qual	DP	Gene	Conseq.Type	phyloP	Phastcons
1	116283343	A	G	rs9428083	.	.	CASQ2	splice_region_variant,regulatory_region_variant,intron_variant	-1.004	0.008
1	116310967	T	C	rs4074536	.	.	CASQ2	missense_variant,regulatory_region_variant	0.591	0.03
1	162313735	C	T	rs3751284	.	.	NOS1AP,MIR556	NMD_transcript_variant,regulatory_region_variant,synonym...	0.655	0.986
1	162335256	C	T	rs348624	.	.	RP11-565P22.6,NOS1AP,C1orf226	2KB_upstream_gene_variant,5_prime_UTR_variant,3_prime_...	0.655	0.999
1	237551376	T	A	rs10754602	.	.	RYR2	intron_variant	0.528	0.044
1	237617757	C	T	rs3763097	.	.	RYR2	synonymous_variant	0.551	0.009
1	237620049	T	C	rs2045955	.	.	RYR2	intron_variant	0.46	0.032
1	237711797	A	G	rs2253273	.	.	RYR2	synonymous_variant	0.655	0.449
1	237814783	C	T	rs684923	.	.	RYR2	synonymous_variant	0.477	0.795
1	237841390	A	G	rs34967813	.	.	RYR2	missense_variant,non_coding_transcript_variant,regulatory_r...	0.591	0.993

Position
Chromosomal location:
1:1-1000000, 2:1-
1000000
Gene:
BRCA2, PPL
SNPId:
rs988179, rs140361978

Population Freqs. +
Quality +
Protein Substitution Scores +
Conservation +
Consequence Type +

Page 1 of 3 > >>

Overview Comments Frequencies Viewer

CASQ2

Graphic weighted between zero and one

We also found 28 variants within the genes defined in our panel.
Maybe we can discover an interesting variant here.

Results: Secondary Findings (Filters)

The image shows a user interface for filtering variants based on secondary findings. It consists of several panels:

- Position**:
 - Chromosomal location: 1:1-1000000, 2:1-1000000
 - Gene: BRCA2, PPL
 - SNPId: rs9988179, rs140361978
- Population Freqs.**:
 - 1000G
 - 1000G Phase3
 - ESP 6500 EA
 - ESP 6500 AA
- Conservation**:
 - phyloP
 - PhastCons
- Consequence Type**: A list of genomic features:
 - Transcript ablation
 - Splice donor variant
 - Splice acceptor variant
 - Stop gained
 - Frameshift variant
 - Stop lost
 - Initiator codon variant
 - Inframe insertion
 - Inframe deletion
 - Missense variant
 - Transcript amplification
 - Splice region variant
 - Incomplete terminal codon variant
 - Synonymous variant
 - Stop retained variant
 - Coding sequence variant
 - ...
- Quality**:
 - QUAL
 - DPA red arrow points to the DP input field.
- Protein Substitution Scores**:
 - SIFT
 - Polyphen

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

Results: Report

We can choose which sections we want to print

Overview Diagnostic Secondary Findings Report

Select to Show

- Generic Data
- Static Filter Resume Table
- Custom Filter Resume Table
- Additional Patient Data
- Editable Conclusions
- Diagnostic Table
- Most Pathogenic Table
- Secondary Findings (with last custom filter used)
- Annex I: Static Filters (decision umbrals)
- Annex II: Panels
 - Diseases
 - Genes
 - Mutations

 Export to PDF/Print

 TEAM Diagnosis

New Diagnosis

Patient Name: _____ Patient Diagnostic: _____

Total Variants	29
Diagnostic Variants	1
Secondary Variants	28

Static Filters Found Variants

T A: Most Likely Pathogenic	0
T B: Potentially Pathogenic	0
T C: Unknown Significance	0
T D: Likely Benign	28

Custom Filter Used Found Variants

No filter used	28
----------------	----

Diagnostic Table

Comments:

Chr	Pos	Ref	Alt	SNP Id	Qual	DP	Gene	Conseq_Type	phyloP	Phastcons	SIFT	Polyphen	MAF 1000G	MAF 1000G Phase 3	ESP6500EA	ESP6500AA	Phenotype	Source
4	11427688	T	C	r328 3775 76	.	.	ANK2	missense_variant .2KB upstream gene_variant.no exon_coding_transcri pt_variant.regulat ory_region_var iant.downstream _gene_variant.int non_variant	-0.768	0.006	0.73	0	.	0.0921	0.1163	0.1859	Cardiac arrhythmia	clinvar

ANNEX I: Static Filters

A: Most Likely Pathogenic --> Sift <=0.05 AND Polyphen>= 0.95

B: Potentially Pathogenic -->

C: Unknown Significance -->

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 your diagnostics in anywhere you want.



More info: publication

Nucleic Acids Research Advance Access published May 26, 2014

Nucleic Acids Research, 2014 **1**
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

Alejandro Alemán^{1,2}, Francisco García-García¹, Ignacio Medina¹ and Joaquín Dopazo^{1,2,3,*}

¹Computational Genomics Department, Centro de Investigación Príncipe Felipe (CIPF), Valencia, 46012, Spain,

²Bioinformatics of Rare Diseases (BIER), CIBER de Enfermedades Raras (CIBERER), Valencia, 46012, Spain and

³Functional Genomics Node, (INB) at CIPF, Valencia, 46012, Spain



More info: TEAM behind the scenes

