

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

Mercedes Medina

September 29th, 2016



**GDA**

International Course on  
Genomic Data Analysis

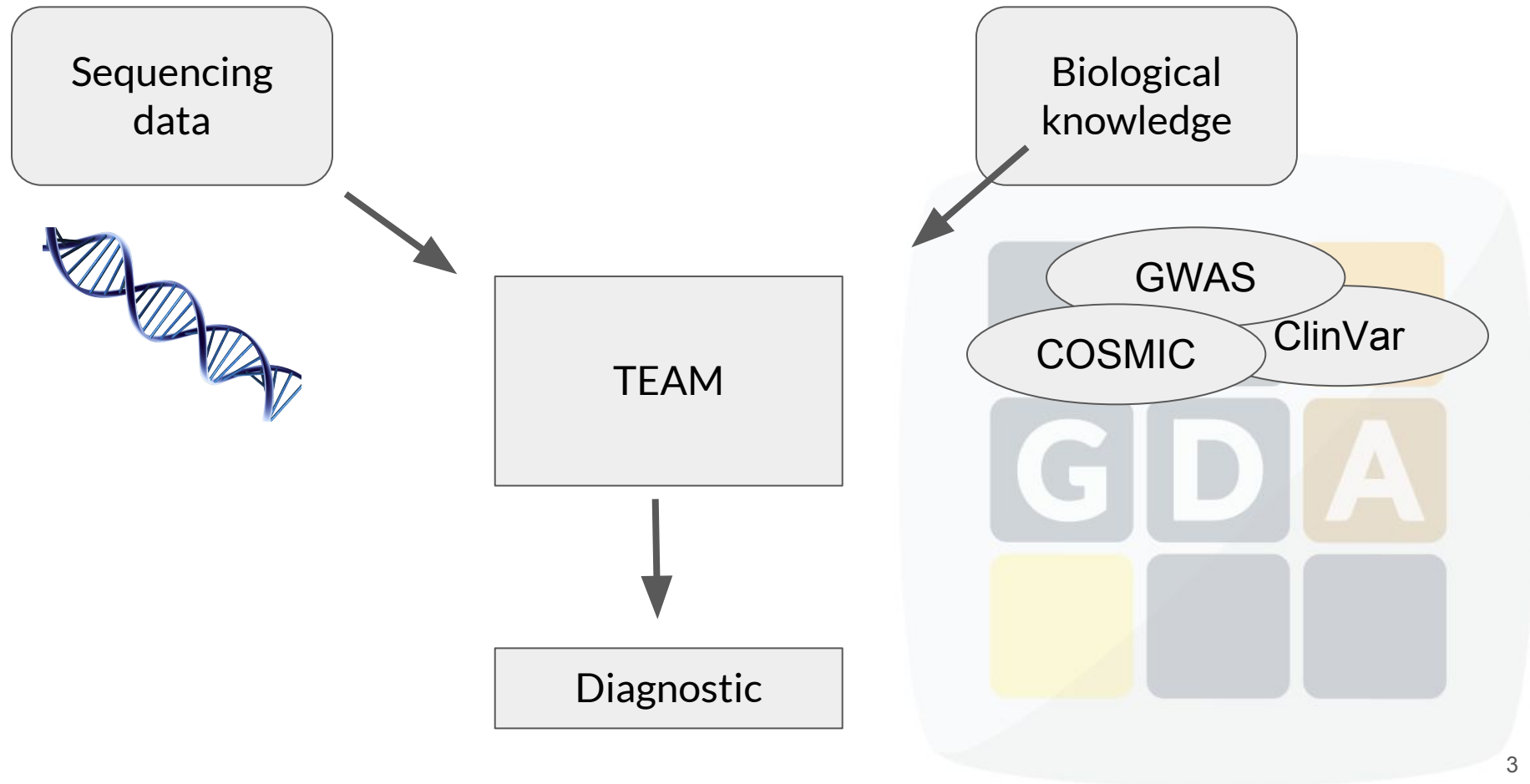


**PRINCIPE FELIPE**  
CENTRO DE INVESTIGACION

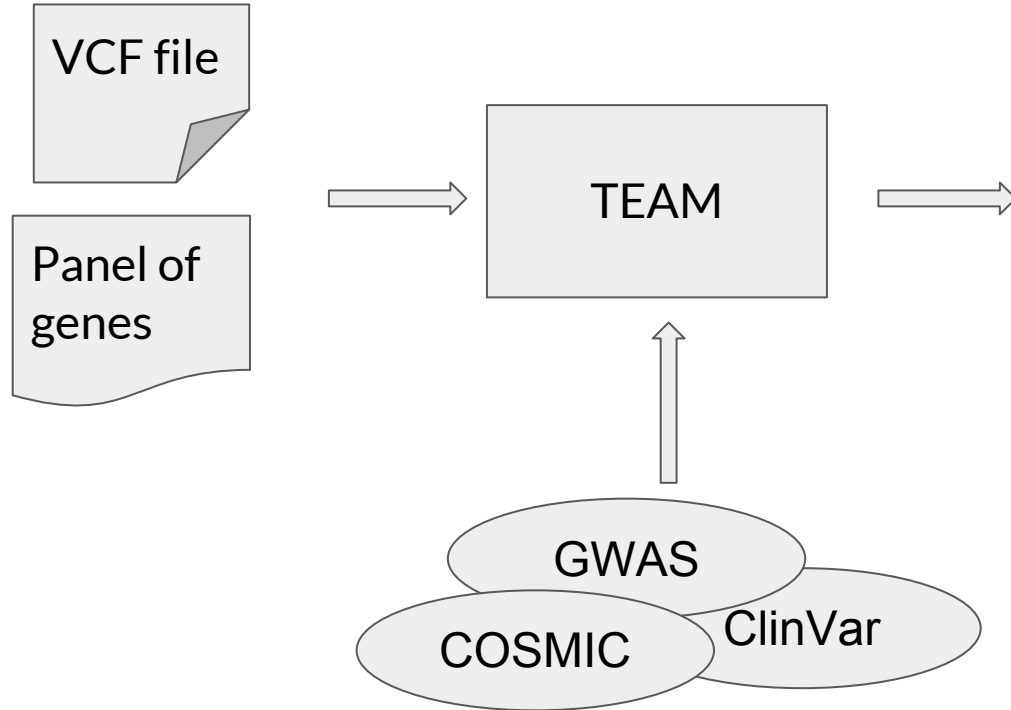
# Introduction

- **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 (**T**argeted **E**nrichment **A**nalysis and **M**anagement)

# 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/>

J. Craig Venter™  
INSTITUTE

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>



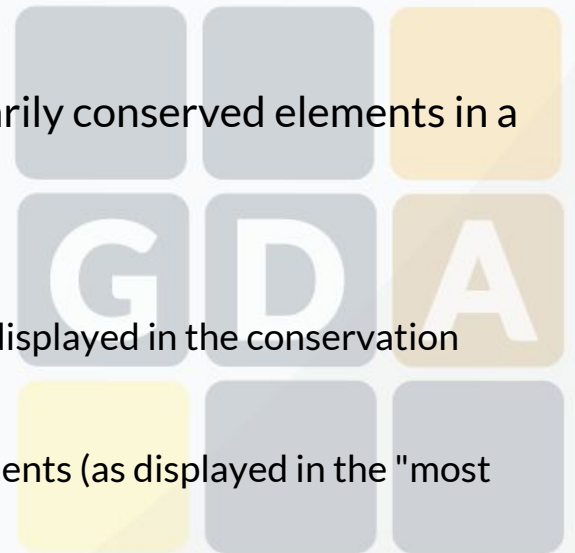
# Getting information: Conservation

## ➤ PhyloP

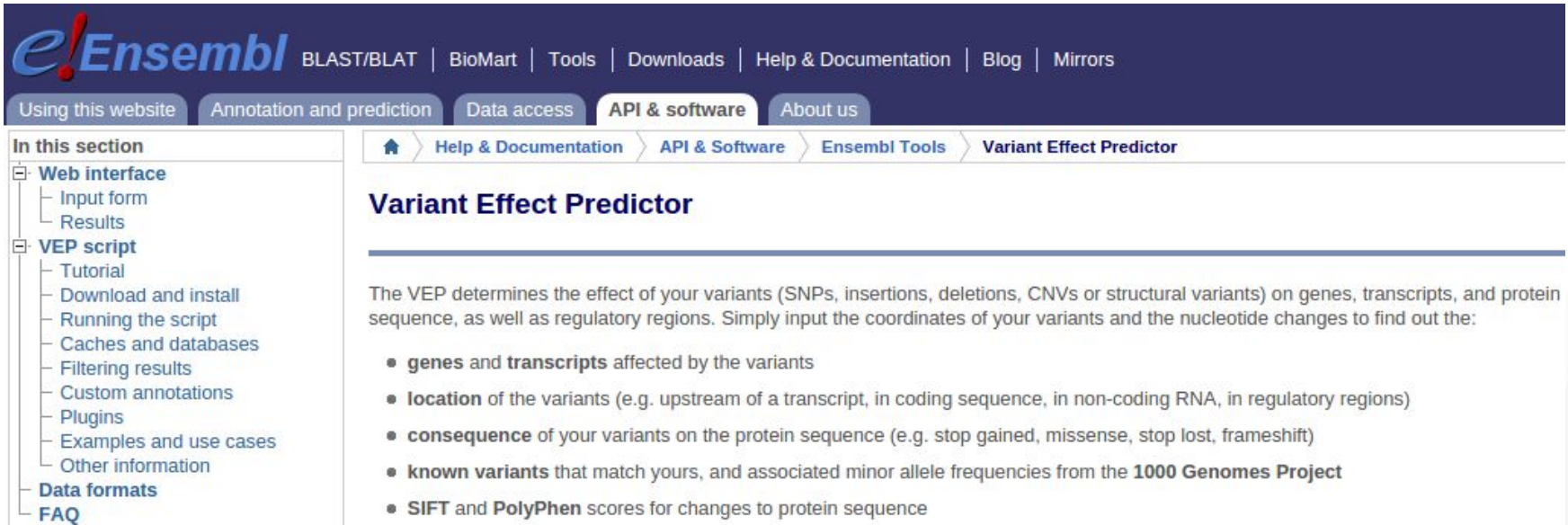
- PhyloP scores measure evolutionary conservation at individual alignment sites. The scores are interpreted as follows compared to the evolution expected under neutral drift:
  - Positive scores -- Measure conservation, which is slower evolution than expected, at sites that are predicted to be conserved.
  - 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



The screenshot shows the Ensembl website's navigation bar with links for BLAST/BLAT, BioMart, Tools, Downloads, Help & Documentation, Blog, and Mirrors. Below this is a secondary navigation bar with tabs for 'Using this website', 'Annotation and prediction', 'Data access', 'API & software', and 'About us'. The 'API & software' tab is active, showing a breadcrumb trail: Home > Help & Documentation > API & Software > Ensembl Tools > Variant Effect Predictor. On the left, a sidebar titled 'In this section' contains a tree view with 'Web interface' (Input form, Results) and 'VEP script' (Tutorial, Download and install, Running the script, Caches and databases, Filtering results, Custom annotations, Plugins, Examples and use cases, Other information). Below the sidebar is a search box labeled 'Search documentation...' and a 'Go' button. The main content area is titled 'Variant Effect Predictor' and contains a paragraph explaining its function: '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:'. This is followed by a bulleted list of information provided by the VEP.

**Variant Effect Predictor**

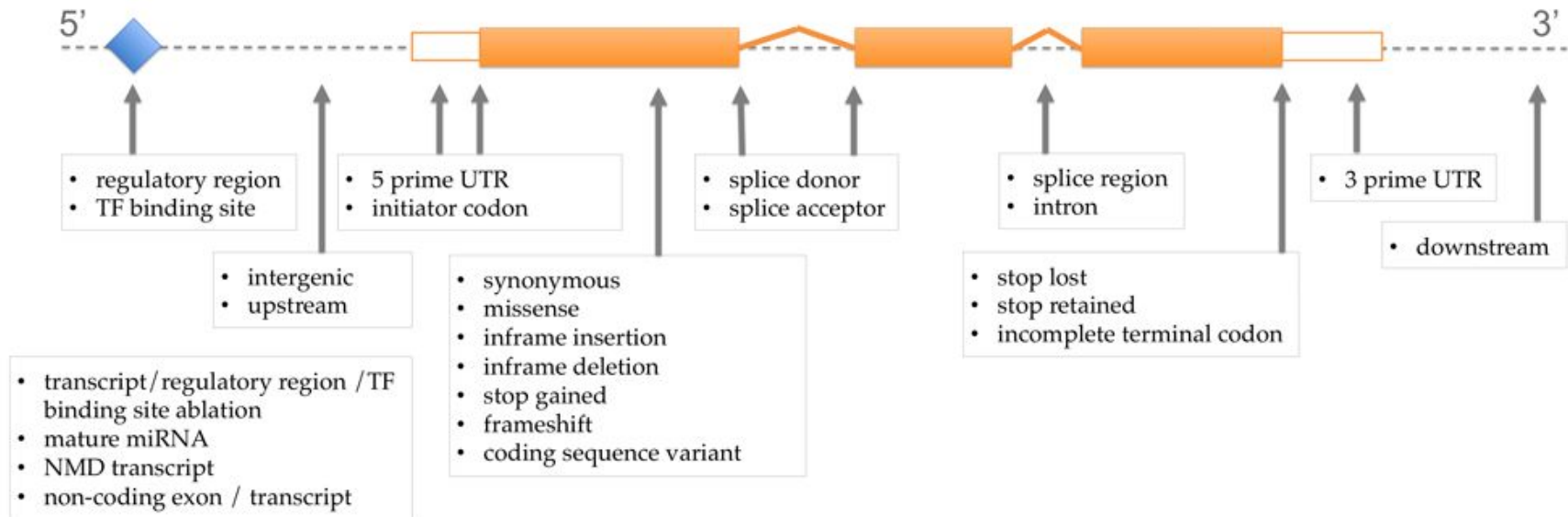
The VEP determines the effect of your variants (SNPs, insertions, deletions, CNVs or structural variants) on genes, transcripts, and protein sequence, as well as regulatory regions. Simply input the coordinates of your variants and the nucleotide changes to find out the:

- **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!](#)





# Getting information: Effect



[http://www.ensembl.org/info/genome/variation/predicted\\_data.html](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/>

TEAM

[home](#) [documentation](#) [tutorial](#) [about](#)

Show Panels

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 (EnsemblId)	Transcript Id	Feature Id	Feature Name	Feature Type	Feature Biotype
---------------------------------	--------	--------------	------------------	------------------	---------------	------------	--------------	--------------	-----------------

# Tool interface: Beta

TEAM 1.1.1


Login Sign up

## 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



Note:

You are currently using chrome/51.0.2704.106 (64-bits) ⓘ

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 2016  
Created by Computational Genomics Department at Centro de Investigación Príncipe Felipe

# Tool interface: Beta

Design/Manage Panels

Data & Diagnoses

TEAM 1.1.1

Run Diagnosis Panels

My data Samples Diagnostics

user 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

**Note:**

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# Panel Manager

You can manage your panels using “Panels”

Search Panel

Edit Panel

Archive Panel

View Panel

The screenshot displays the TEAM 1.1.1 Panel Manager interface. The top navigation bar includes links for Run Diagnosis, Panels, My data, Samples, and Diagnostics, along with user profile and logout options. The main content area is divided into three sections: User Panel List, Panel Preview, and Example Panel List.

**User Panel List:** This section contains a search bar and a list of panels. The 'retinitis' panel is selected. Red arrows point to the search bar (labeled 'Search Panel'), the edit icon (labeled 'Edit Panel'), and the archive icon (labeled 'Archive Panel') for the 'retinitis' panel.

**Panel Preview:** This section shows details for the 'retinitis' panel, including its name, author, version, and description. It also displays a table of diseases, genes/regions, and mutations.

Diseases	Genes/Regions	Mutations	
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
PRPH2	6	42664340	42690312
PDE6B	4	619373	664571
LOC102723833	.	.	.
RDH12	14	68168603	68201169

**Example Panel List:** This section shows a list of example panels, including 'retinitis'. A red arrow points to the 'View Panel' button (labeled 'View Panel').

At the bottom of the interface, there are buttons for '+ New Panel' and 'Export panel to PDF/Print'.

# Panel Manager: Create a Panel

**TEAM 1.1.1** Run Diagnosis Panels My data Samples Diagnostics test profile logout

### User Panel List

Main Archived

Search by name...

- asthma
- cardiac
- retinitis**
- CMT
- hypercholesterolemia
- cataratas
- Hyperammonaemia
- osteogenesis
- fanconi
- Ketotic

### Example Panel List

retinitis

**+ New Panel**

Export panel to PDF/Print

### Panel Preview

Name: **retinitis**  
Author: aaleman  
Version: 1  
Description:

Diseases	Genes/Regions	Mutations	
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
PRPH2	6	42664340	42690312
PDE6B	4	619373	664571
LOC102723833	.	.	.
RDH12	14	68168603	68201169

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Create a  
New Panel

Export or  
Print a  
Panel

# Panel Designer: Diseases

Write the phenotypes you are interested in.

+ New Panel

Step 1 of 4: Select Diseases

Step 2

Phenotype	Source
retinitis	
AIPL1-Related Retinitis Pigmentosa	clinvar
Ataxia and retinitis pigmentosa with isolated vitamin e deficiency	clinvar
Fundus albipunctatus , RETINITIS PUNCTATA ALBESCENS, PERIP...	clinvar
Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentos...	clinvar
Juvenile retinitis pigmentosa, AIPL1-related	clinvar
MICROPHthalmia, POSTERIOR, WITH RETINITIS PIGMENTO...	clinvar
Neuropathy ataxia retinitis pigmentosa syndrome	clinvar
Polynuropathy, hearing loss, ataxia, retinitis pigmentosa, and cata...	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
Retinitis pigmentosa 14	clinvar

1 - 16 of 83

Add

Phenotype	Source
-----------	--------

1 - 0 of 0

Clear

Next »



# Panel Designer: Diseases

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

+ New Panel

Step 1 of 4 : Select Diseases

Step 2

Phenotype	Source
retinitis	▼
AIPL1-Related Retinitis Pigmentosa	clinvar
Ataxia and retinitis pigmentosa with isolated vitamin e deficiency	clinvar
fundus albipunctatus, RETINITIS PUNCTATA ALBESCENS, PERIP...	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 cata...	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
Retinitis pigmentosa 14	clinvar

1 - 16 of 83

Add

Phenotype	Source
Loading...	

1 - 0 of 0

Clear

Next »

Click "Add"

# Panel Designer: Diseases

+ New Panel

Step 1 of 4 : Select Diseases

Step 2

Phenotype	Source
retinitis	
AIPL1-Related Retinitis Pigmentosa	clinvar
Ataxia and retinitis pigmentosa with isolated vitamin e deficiency	clinvar
fundus albipunctatus , RETINITIS PUNCTATA ALBESCENS, PERIP...	clinvar
Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentos...	clinvar
Juvenile retinitis pigmentosa, AIPL1-related	clinvar
MICROPTHALMIA, POSTERIOR, WITH RETINITIS PIGMENTO...	clinvar
Neuropathy ataxia retinitis pigmentosa syndrome	clinvar
polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cata...	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
Retinitis pigmentosa 14	clinvar

« < Page 1 of 6 > »

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Add

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

« < Page 1 of 1 > »

1 - 5 of 5

Clear

Next »

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

+ New Panel

Step 1 Step 2 of 4 : Select Genes Step 3

Diseases Selected:

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

Genes/Regions

BRCA2 , PPL

Add Genes

Import from BED

Import

Import from other Panel

View Panel Import

Import from external App

- Panel App Import

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

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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.

The screenshot shows the 'Panel Designer: Genes' interface with four main sections for adding genes:

- Genes/Regions:** A text input field containing 'BRCA2 , PPL' and an 'Add Genes' button.
- Import from BED:** An 'Import' button.
- Import from other Panel:** A dropdown menu, a 'View Panel' button, and an 'Import' button.
- Import from external App:** A list showing 'Panel App' and an 'Import' button.

Other way is using PanelApp tool

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	✕

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Clear

# Panel Designer: Genes (BED file)

Choose a BED  
file

Import genes

Check errors or  
warnings

Choose file...

Selected file name: file.bed

Import

Revalidate

File validation log:

Line	Type	Message
------	------	---------

100 % Stop

Errors: 0 Warning: 0 Info: 0 Lines: 10

# Panel Designer: Genes (PanelApp)

**Import From PanelApp**

Disease	N°Genes	Version
conge	filter by N°Genes	filter by Version
Congenital myopathy	66	0.3
Congenital myaesthesia	17	0.0
Congenital neutropaenia	15	1.16
Congenital hearing impairment (profound/s...	348	1.5
Paediatric congenital malformation-dysmor...	62	1.2
Congenital muscular dystrophy	38	0.0
Congenital adrenal hypoplasia	18	0.36
Autosomal recessive congenital ichthyosis	12	1.0
Beckwith-Wiedemann syndrome (BWS) and...	9	1.8
Congenital heart disease	19	0.5
Congenital hypothyroidism or thyroid agene...		0.0

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1 - 11 of 13

>>More info <<

Gene	Level Of Confidence
CHAT	HighEvidence
CHRNA1	HighEvidence
CHRN B1	HighEvidence
CHRND	HighEvidence
CHRNE	HighEvidence
DOK7	HighEvidence
GFPT1	HighEvidence
MUSK	HighEvidence
RAPSN	HighEvidence
SCN4A	HighEvidence
COLQ	ModerateEvidence
DPAGT1	ModerateEvidence
AGRN	LowEvidence
ALG2	LowEvidence

Total: 17

Add Genes

<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**

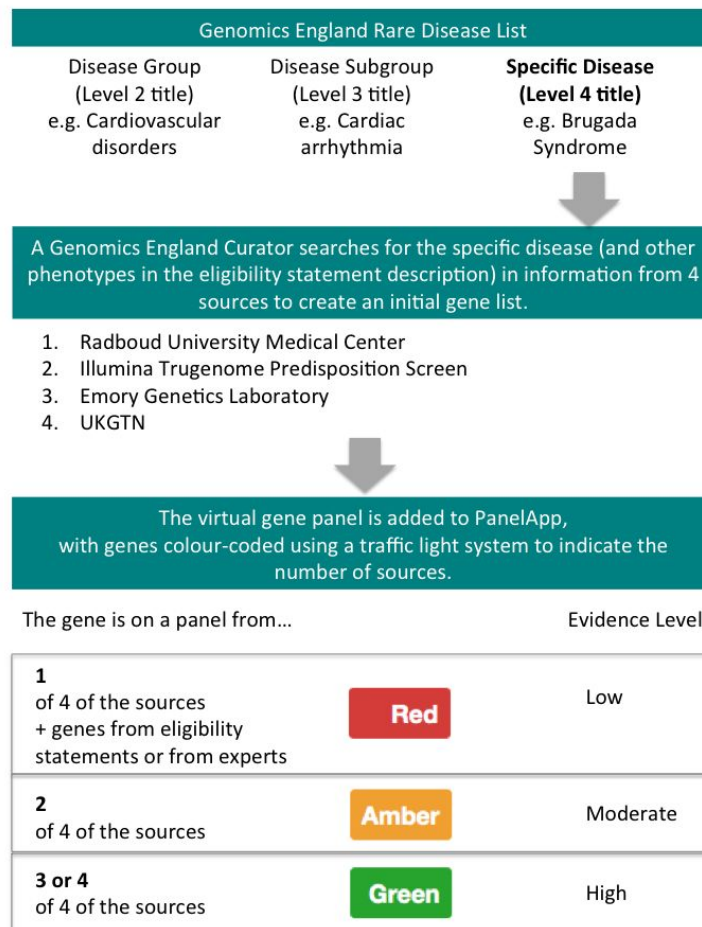
High, diagnostic-grade gene that will be used to Interpret genomes.

**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

**+ New Panel**

**Step 3 of 4 : Select Mutations**

Step 2 Step 4

Diseases Selected:

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

Genomic Pos. —

Chr: Pos: Ref: Alt: Phe: Open Genome Browser Add

Import VCF —

Phe: Import

Import CSV —

Separator: ; Ignore first line (header): ☒ Choose File No file chosen Import

Import from other Panel —

View Panel Import

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	23180400	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	✕

1 - 15 of 491

Clear

« Previous Next »



# 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

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	
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	✕

Importing mutations from other virtual panels is supported too.

# Panel Designer: Mutations

View Mutation

Chr: 1 Pos: 1004553 Ref: C Alt: G Disease Name: My Disease

Reset Check Add Mutation

Min Max 77 1:1004515-1004591 Go! << < > >>

Region overview Window size: 615 nts

1004246 1004553 1004860

Detailed information Window size: 77 nts

1004515 1004553 1004591

Sequence - v ^

ATCAGCAGCCCCGCCCTGCCGGCACCTTCCCCCATCCGTAGCCCCCTCCCCAAGCGGCTTGTCCGCAGGGC

Gene - v ^

SNP - v ^

rs189753683 rs371314094 rs75134978

Powered by Genome Maps C 1:1004583

Import mutation

Search mutation

# Panel Designer: Panel info

The name of  
the Panel

The author/  
date/  
description

Step 4 of 4 : Panel Info

Name  
\_2

Author

Date  
mm/dd/yyyy

Description

Save

« Previous

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.

TEAM 1.1.1 Run Diagnosis Panels My data Samples Diagnostics test profile logout ?

Step 1 of 3 : Choose a Sample Step 2

/family > fam1

Upload Search by name...

Name	Status	Source	Suspected	Diagnosis
HG01500	✓ READY	HG01500_HG0150...	Retinitis	
HG01501	✓ READY	HG01500_HG0150...	Retinitis	
HG01500_HG0...	✓ READY	HG01500_HG0150...	Retinitis	
HG01500_HG0...	✓ READY	HG01500_HG0150...	Add	
HG01500_HG0...	✓ READY	HG01500_HG0150...	Add	

Study Type: FAMILY

Next >

Add Suspected  
Diagnosis

Next Step

# New Diagnosis

Select the panel to be used.

Step 1

Step 2 of 3 : Choose a Panel

Step 3

User Panel List

asthma

cardiac

retinitis

CMT

hypercholesterolemia

cataratas

Hyperammonaemia

osteogenesis

fanconi

Ketotic

Panel Preview

Name: retinitis

Author: aaleman

Version: 1

Description:

Diseases		Genes/Regions		Mutations	
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	213032155	A	G	Retinitis pigmentosa	clinvar
1	213032515	G	A	Retinitis pigmentosa	clinvar

Example Panel List

retinitis

+ New Panel

<< < Page 1 of 26 > >>

1 16 of 411

<< Previous

Next >>

Next Step

# New Diagnosis

TEAM 1.1.1 [Run Diagnosis](#) [Panels](#) [My data](#) [Samples](#) [Diagnostics](#) [test](#) [profile](#) [logout](#) [?](#)

Step 3 of 3: Job information

Job name  
TEAM Diagnosis

Description  
New Diagnosis

Run

« Previous

Give a name to the new diagnosis/job

Push "Run"

# 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.

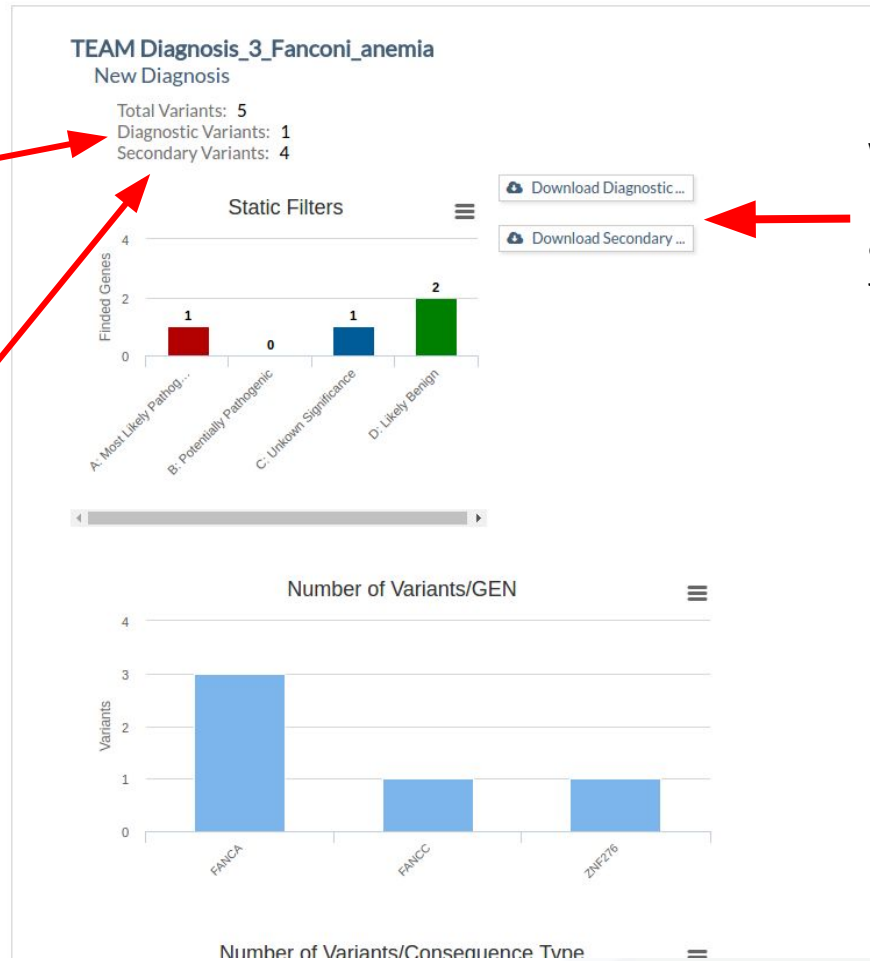
The screenshot shows the 'Diagnoses Browser' window. The top navigation bar includes 'files', 'Diagnostics' (highlighted with a red box), 'test', 'profile', 'logout', and a help icon. The left sidebar shows a tree view with 'Default project', 'Default study', 'family', 'fam1' (selected), 'family2', 'fam2', 'family3', and 'fam3'. The main panel displays a list of diagnostic runs. The first row is 'TEAM Diagnosis' with status 'Running' and timestamp '02/28/2016 19:17:55'. The following rows are 'TEAM Diagnosis' with status 'Ready' and various timestamps. The last three rows are 'TEAM Diagnosis' with status 'Error' and various timestamps. The interface also includes a search bar and status filters (All, Running, Ready, Error).

Diagnosis Name	Status	Timestamp
TEAM Diagnosis	Running	02/28/2016 19:17:55
TEAM Diagnosis	Ready	02/26/2016 16:30:46
TEAM Diagnosis	Ready	02/26/2016 16:29:16
TEAM Diagnosis	Ready	02/26/2016 16:29:16
TEAM Diagnosis	Ready	02/26/2016 16:29:15
panelTestMother	Ready	02/26/2016 16:22:32
TEAM Diagnosis	Error	02/26/2016 12:59:15
TEAM Diagnosis	Error	02/26/2016 12:58:33
panelTestMother	Error	02/26/2016 12:53:35
pather	Error	02/26/2016 12:49:39
TEAM Diagnosis	Error	02/26/2016 12:48:45

# 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

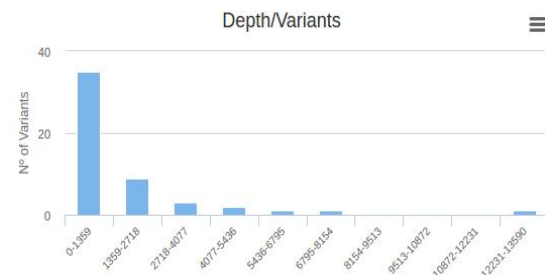
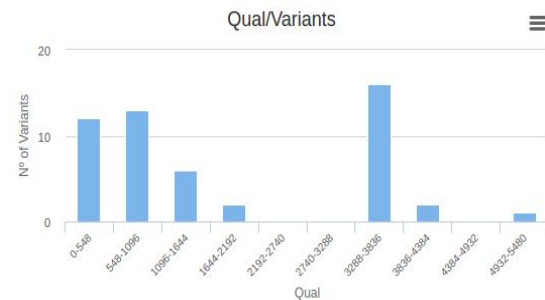
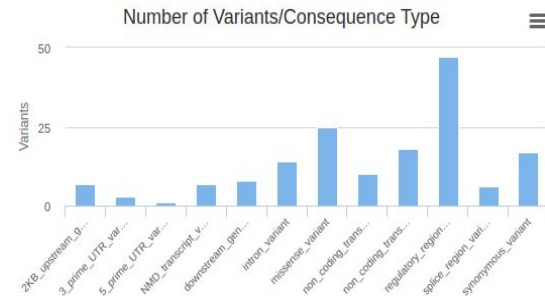
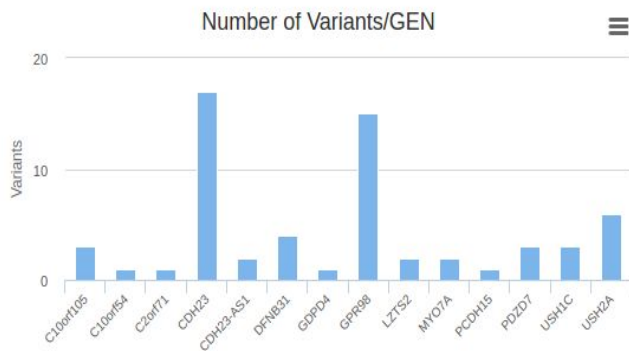
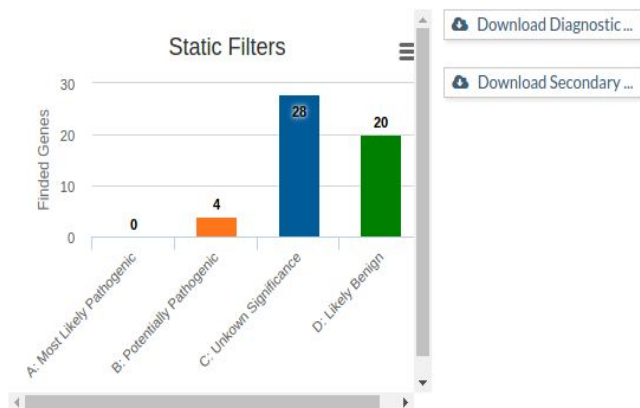
## TEAM Diagnosis\_RP\_905\_Usher

New Diagnosis

Total Variants: 52

Diagnostic Variants: 0

Secondary Variants: 52



# Results: Diagnostic Variants



Overview

Diagnostic



Secondary Findings

Report

Diagnostic

Chr	Pos	Ref	Alt	Gt	Gene	Conseq. Type	phyloP	Phastco...	SIFT	Polyphen	MAF 10...	ESP 6500	Beacon	OMIM	Phenotype	Source
X	38240670	C	T	1/1	TM4SF2.OTC	missense_variant,non_coding_transcript_exon_variant,non_c...	0.486	0.902	0.16	0.03	0.0003	0.0001			Hyperammonaemia	clinvar

1 - 1 of 1



Variant Data

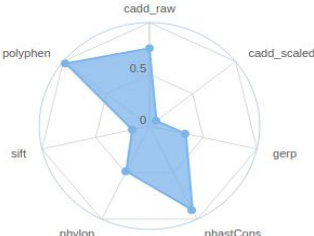
Overview


Comments

Frequencies

Genome Viewer

X:38240670:C:T



 All values are normalized between zero and one.  
- Values closest to zero are deleterious and closest to one are benign.  
- Polyphen and Sift are opposed, but in this case, Polyphen has been calculated as 1 - Polyphen.

We found a diagnostic variant. It appears in Clinvar.

# Results: Variant Data

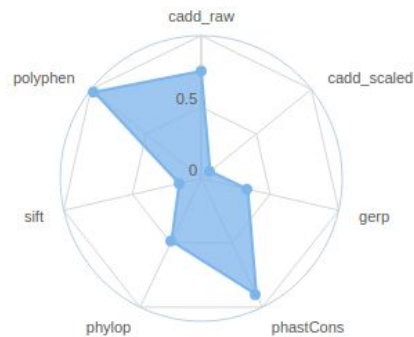
## Variant Data



## Variant Data

Overview Comments Frequencies Genome Viewer

X:38240670:C:T

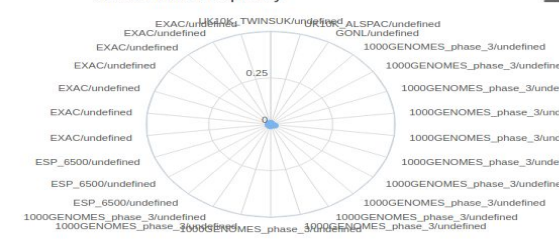


## Variant Data

Overview Comments Frequencies Genome Viewer

Study	Population	SuperPopulation	Ref. Allele	Alt. Allele	Ref. Allele Fr.	Alt. Allele Fr.	MAF	O/O	O/I	I/I
UK10K_TWINSUK			G	A	0.997	0.003	0.003			
UK10K_ALSPAC			G	A	0.992	0.008	0.008			
GONL			G	A	0.995	0.005	0.005			
1000GENOMES_phase_3			G	A	0.997	0.003	0.003	0.99...	0.00...	0
1000GENOMES_phase_3			G	A	0.998	0.002	0.002	0.99...	0.00...	0
1000GENOMES_phase_3			G	A	0.995	0.005	0.005	0.98...	0.01...	0
1000GENOMES_phase_3			G	A	0.995	0.005	0.005	0.99...	0.00...	0
1000GENOMES_phase_3			G	A	0.999	0.001	0.001	0.99...	0.00...	0
1000GENOMES_phase_3			G	A	0.981	0.019	0.019	0.96...	0.03...	0
1000GENOMES_phase_3			G	A	0.995	0.005	0.005	0.98...	0.01...	0

## Minor Allele Frequency



# Results: Secondary Findings

Overview Diagnostic **Secondary Findings** Report

Variant Filters

Static Filters Custom Filters

Without Filters 4

A: Most Likely Pathogenic 1

B: Potentially Pathogenic 0

C: Unknown Significance 1

D: Likely Benign 2

Secondary Findings

Chr	Pos	Ref	Alt	Gt	SNP Id	Qual	Gene	Conseq. Type	phyloP	PhastC...	SIFT	Polyph...	MAF 1000G Phas...	ESP 6500	Spanish MAF	EXAC	Beacon	OMIM	Clinvar
9	98011497	G	A	1 0	rs1800361	100.000	FANCC	missense_variant,non_coding_transcript_exon...	-0.143	0.971	0.02	0.998	0.0026	0.005	0.007	0.0047			Hereditary ca
16	89806347	A	T	1 0	rs7195906	100.000	ZNF276.FANCA	2KB_upstream_gene_variant,non_coding_tran...	0.555	0.009			0.2935		0.344	0.4773			
16	89836323	C	T	1 1	rs7195066	100.000	FANCA	missense_variant,2KB_upstream_gene_varian...	-0.385	0.002	0.3	0	0.3333	0.4307	0.327	0.469			
16	89866043	T	C	1 1	rs7190823	100.000	FANCA	missense_variant,2KB_upstream_gene_varian...	0.555	0.145	1	0	0.3095	0.494	0.357	0.4834			

Variant Data

Overview Comments Frequencies Genome Viewer

9:98011497:G:A

Legend:

- All values are normalized between zero and one.
- Values closest to zero are deleterious and closest to one are benign.
- Polyphen and Sift are opposed, but in this case, Polyphen has been calculated as 1 - Polyphen.

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

Overview Diagnostic

Variant Filters

Static Filters Custom Filters

Clear Search

Position +

Population Freqs. +

Genotype +

Quality +

Protein Substitution Scores +

Conservation +

Consequence Type +

Second

Variant

Overview

You can see filters used previously in Filters History

Static Filters Custom Filters

Clear Search

Clear

Date	Name	Found
20/7 16:14	Qual > 10000	2
20/7 16:14	Consequence Types: splice_acceptor_variant,splice_...	0
20/7 16:13	GT=heter AND MAF 1000GP3 < 0.025	1
20/7 16:13	Chromosomal Location: (13) AND Genes: (BRCA2) ...	5

Chr Pos Ref Alt Gt SNP Id Qual

17	41251931	G	A	1/1	rs799923	17483.0
						14325.0

Variant Data

Overview Comments Frequencies Genome

Search variants with selected params

# Results: Secondary Findings (Filters)

**Position**

Chromosomal location:  
1:1-1000000,2:1-1000000

Gene:  
BRCA2 , PPL

SNPId:  
rs9988179,rs140361978

**Genotype**

☒ Heterozygous 5

☐ Homozygous 5

**Quality**

QUAL  
> 10000

DP  
> 0

**Population Freqs.**

1000G Phase 3  
< 0.01

ESP 6500  
< 0

Spanish MAF  
< 0.225

EXAC  
< 0

**Protein Substitution Scores**

SIFT  
< 0.05

Polyphen  
> 0.7

CADD  
< 0.075

**Conservation**

PhyloP  
< 0

PhastCons  
< 0.003000

**Consequence Type**

» High

» Moderate

☐ inframe\_insertion 0

☐ inframe\_deletion 0

☐ missense\_variant 25

☐ inframe\_insertion 0

☐ inframe\_deletion 0

☐ missense\_variant 3

» Low

☐ splice\_region\_variant 6

☐ synonymous\_variant 17

☐ stop\_retained\_variant 0

☐ splice\_region\_variant 0

☐ synonymous\_variant 2

☐ stop\_retained\_variant 0

» Modifier

Number of variants found in each category

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



# 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

OverviewDiagnosticSecondary FindingsReport

Select to Show

- ☒ Patient data
- ☒ Generic data
- ☒ Static filter resume
- ☒ Custom filter resume
- ☐ Editable conclusions
- ☒ Diagnostic table
- ☐ Most pathogenic table
- ☐ Secondary findings (with last custom filter used)
- ☒ Panel used

Save report

Export report to PDF/Print

Export panel to PDF/Print

Team report

Cellbase v4 9/16/2016, 3:23:05 PM

Job name: TEAM Diagnosis\_3\_Fanconi\_anemia  
Job description: New Diagnosis

Patient data

Patient ID: 1234

Instrument: Illumina

Analyzed by: test

Sample Origin:

Patient Suspected Diagnosis: b

Patient Diagnosis: Fanconi anemia, complementation group q

Generic data

Total Variants: 5

Diagnostic Variants: 1

Secondary Variants: 4

Static filter resume

Variants found with static filters:

A: Most Likely Pathogenic: 1

B: Potentially Pathogenic: 0

C: Unknown Significance: 1

D: Likely Benign: 2

Static filters description:

A: Most Likely Pathogenic: Sift least than 0.05 and Polyphen bigger than 0.95

# Who is using TEAM?

*ciberer* *isciii*

Centro de Investigación Biomédica en Red  
*Enfermedades Raras*

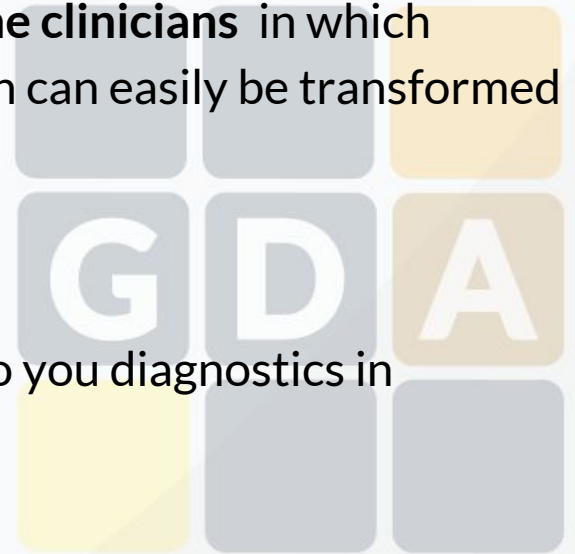
IT4Innovations  
national!\$11€0  
supercomputing  
center1001\$1\$0





# 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**

*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<sup>1,2</sup>, Francisco Garcia-Garcia<sup>1</sup>, Ignacio Medina<sup>1</sup> and Joaquín Dopazo<sup>1,2,3,\*</sup>**

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

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

<sup>3</sup>Functional Genomics Node, (INB) at CIPF, Valencia, 46012, Spain

## More info: TEAM behind the scenes

