

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

Mercedes Medina

September 29th, 2016



GDA

International Course on
Genomic Data Analysis

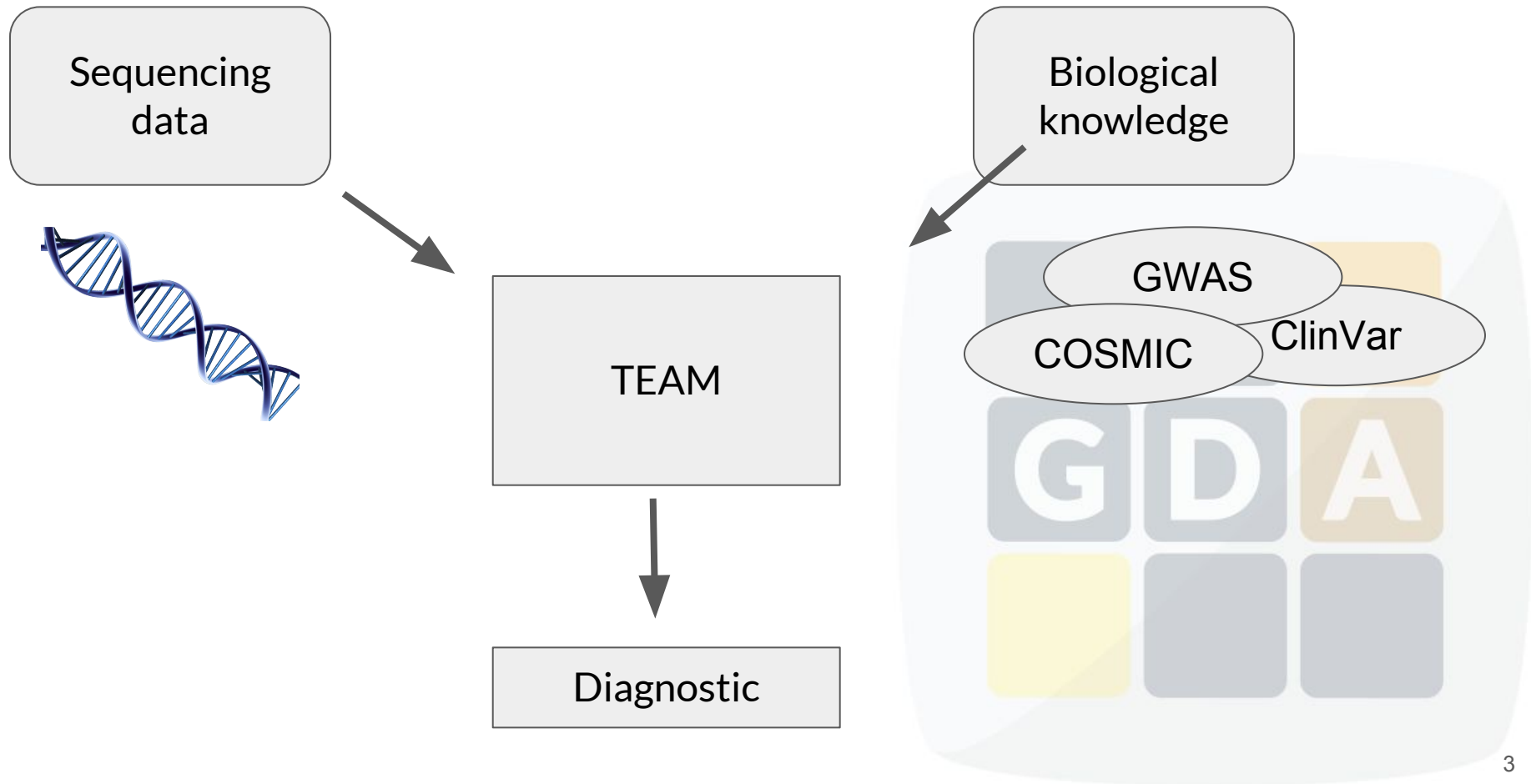


PRINCIPE FELIPE
CENTRO DE INVESTIGACION

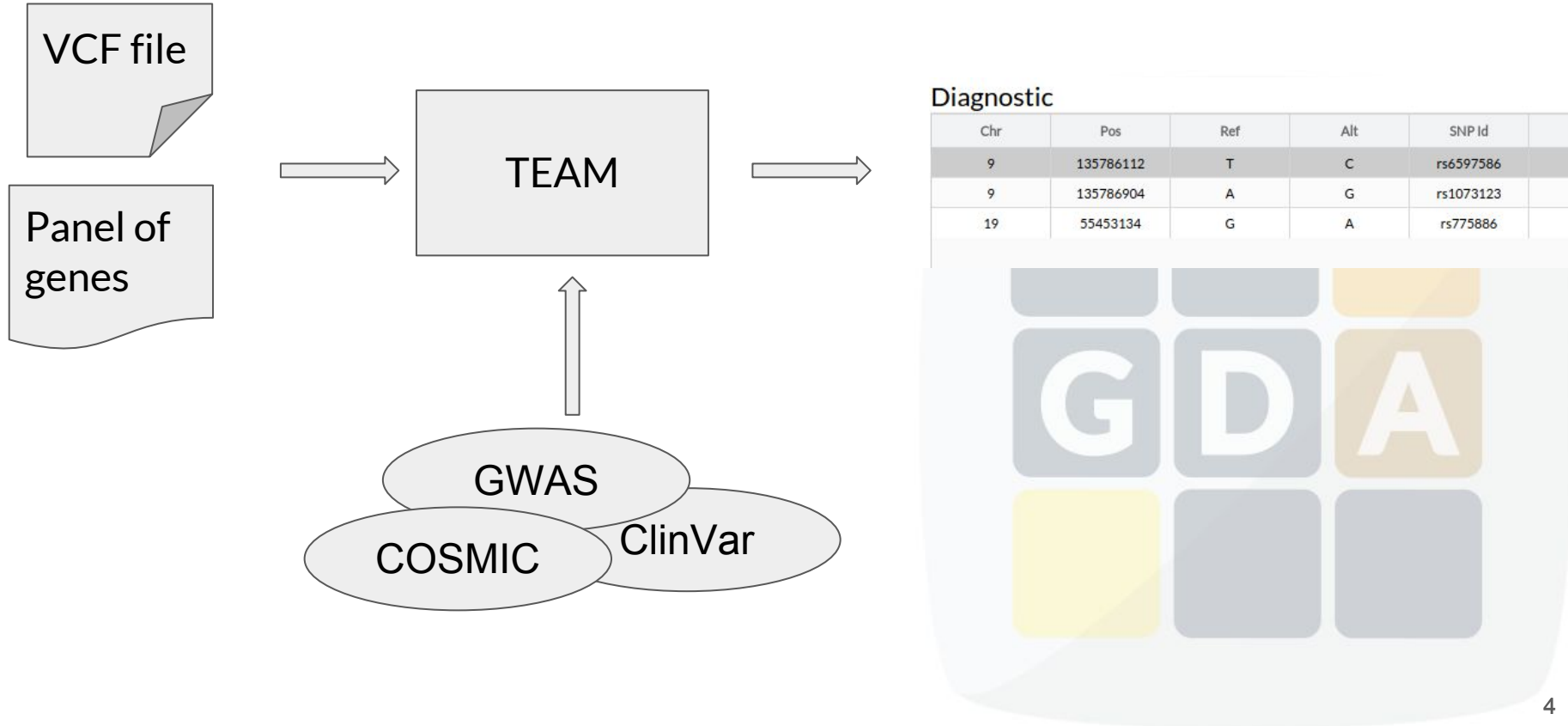
Introduction

- **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?



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>



PolyPhen

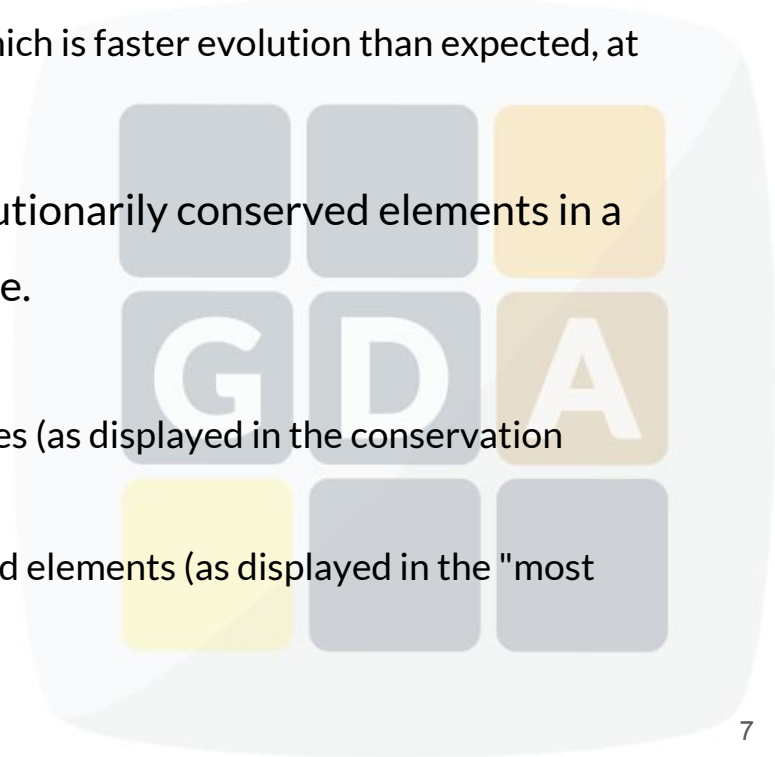
Getting information: Conservation

➤ PhyloP

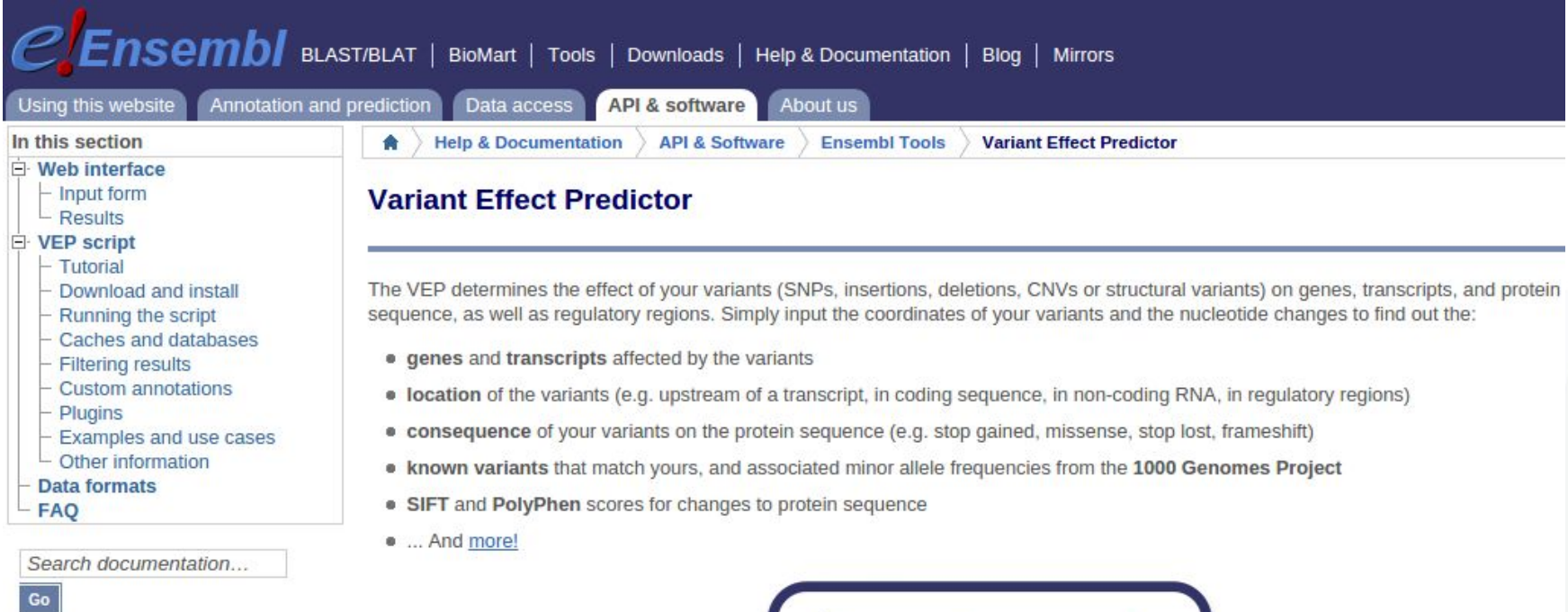
- PhyloP scores measure evolutionary conservation at individual alignment sites. The scores are interpreted as follows compared to the evolution expected under neutral drift:
 - Positive scores -- Measure conservation, which is slower evolution than expected, at sites that are predicted to be conserved.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



The screenshot shows the Ensembl website navigation and the VEP documentation page. The top navigation bar includes 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, and a breadcrumb trail shows the path: Home > Help & Documentation > API & Software > Ensembl Tools > Variant Effect Predictor.

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...
Go

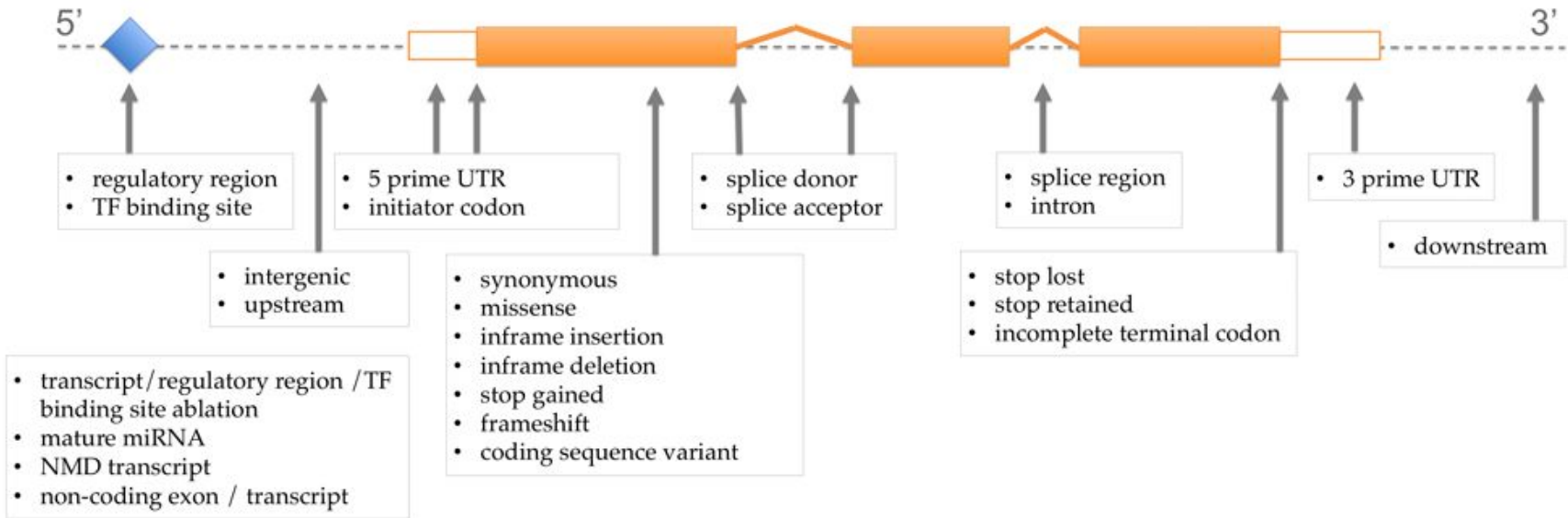
Variant Effect Predictor

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

Inputs: Panel + VCF

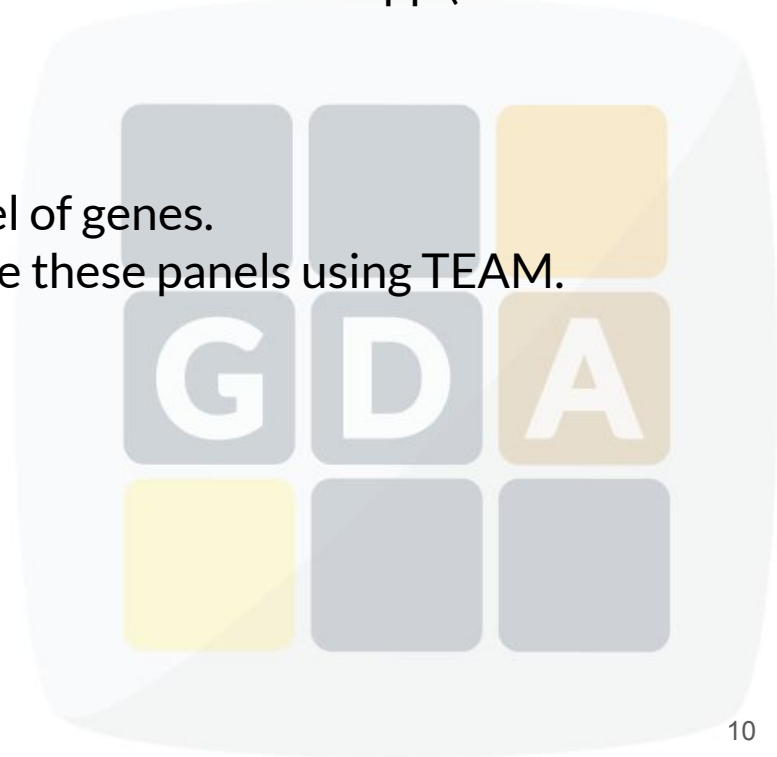
TEAM needs a:

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:

VCF File:

Results

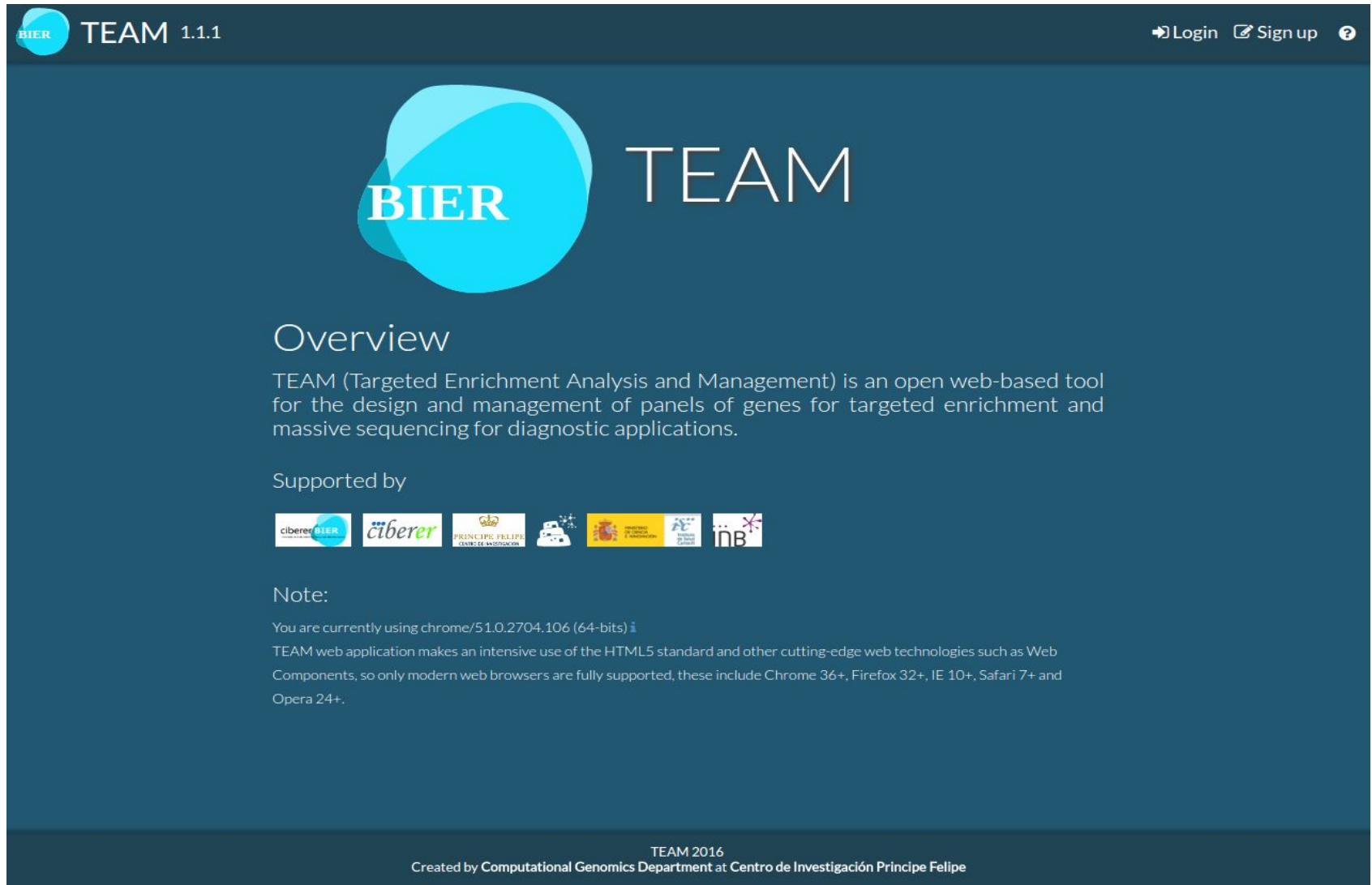
Diagnostic Secondary findings

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

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




BIER TEAM 1.1.1 [Login](#) [Sign up](#)

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:

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:

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

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 interface. The top navigation bar includes 'Run Diagnosis', 'Panels', 'My data', 'Samples', and 'Diagnostics'. The user is logged in as 'test'.

User Panel List

Search by name...

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

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

1 - 19 of 32

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

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

Example Panel List

retinitis

+ New Panel

Export panel to PDF/Print

Page 1 of 2

1 - 19 of 32

Create a New Panel

Export or Print a Panel

Panel Designer: Diseases

Write the phenotypes you are interested in.

Step 1 of 4: Select Diseases

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

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

1 - 16 of 83

1 - 0 of 0

Next »

Panel Designer: Diseases

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

Step 1 of 4: Select Diseases

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

Step 2

Phenotype	Source
Loading...	

1 - 0 of 0

Clear

Next »

Click "Add"

Panel Designer: Diseases

+ New Panel x

Step 1 of 4 : Select Diseases Step 2

Phenotype	Source	
retinitis	<input type="text" value=""/>	
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

Phenotype	Source	
Retinitis pigmentosa 1	clinvar	<input checked="" type="checkbox"/>
Retinitis pigmentosa 10	clinvar	<input checked="" type="checkbox"/>
Retinitis pigmentosa 11	clinvar	<input checked="" type="checkbox"/>
Retinitis pigmentosa 12	clinvar	<input checked="" type="checkbox"/>
Retinitis pigmentosa 13	clinvar	<input checked="" type="checkbox"/>

1 - 5 of 5

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

Step 2 of 4: Select Genes

Diseases Selected:

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

Genes/Regions

BRCA2, PPL

Import from BED

Import from other Panel

Import from external App

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	✕
ANKK1	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

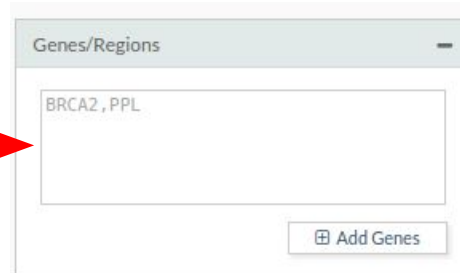
1 - 15 of 35

Clear

« Previous Next »

Panel Designer: Genes

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

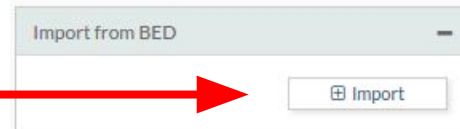


Genes/Regions

BRCA2 , PPL

Add Genes

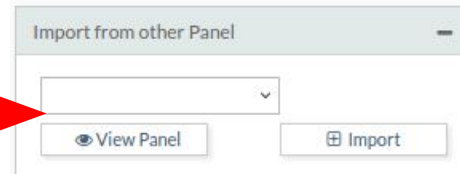
Adding regions through a BED file is also supported



Import from BED

Import

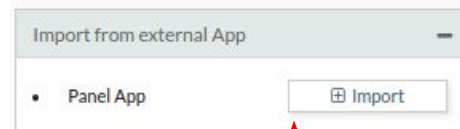
We can import genes from other virtual panels already created.



Import from other Panel

View Panel

Import



Import from external App

Panel App

Import

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	✕

Page 1 of 3

1 - 15 of 35

Clear

Panel Designer: Genes (BED file)

Choose a BED file



Import genes



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

Check errors or warnings



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

« Page 1 of 2 » 1 - 11 of 13 >>More info <<

Gene	Level Of Confidence
CHAT	HighEvidence 🟢
CHRNA1	HighEvidence 🟢
CHRNB1	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

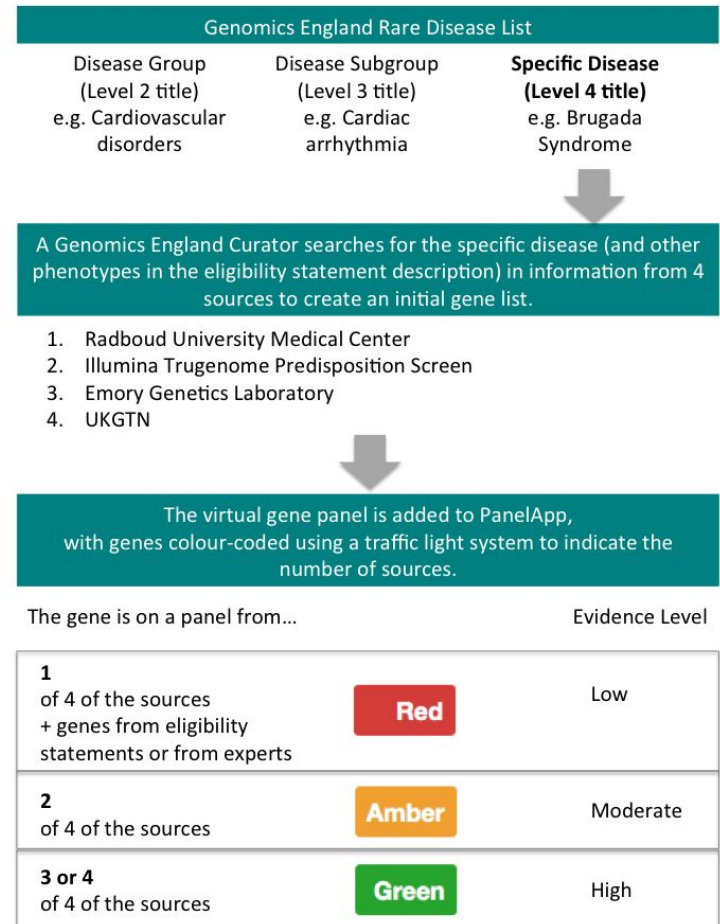
A crowdsourcing tool to allow gene panels to be shared, downloaded, viewed and evaluated by the Scientific Community

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

Step 3 of 4: Select Mutations

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:

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	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	✕

Page 1 of 33

1 - 15 of 491

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

Region overview Window size: 615 nts

1004246 1004553 1004860

Detailed information Window size: 77 nts

1004515 1004553 1004591

Sequence - v ^

ATCAGCAGCCCCGCCCTGCCGGCACCTTCCCCCATCCGTAGCCCCCTCCCAAGCGGCTTGTCCGCAGGGC

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

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

Step 1 of 3 : Choose a Sample Step 2M

/family > fam1

Upload

Name	Status	Source	Suspected	Diagnosis
HG01500	✓ READY	HG01500_HG01500...	Retinitis	
HG01501	✓ READY	HG01500_HG01500...	Retinitis	
HG01500_HG0...	✓ READY	HG01500_HG01500...	Retinitis	
HG01500_HG0...	✓ READY	HG01500_HG01500...		Add
HG01500_HG0...	✓ READY	HG01500_HG01500...		Add

Study Type: FAMILY

Next >

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.

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 of 411

« Previous Next »

Next Step

New Diagnosis

BIER 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 displays the 'Diagnostics' section of a software interface. At the top, there is a navigation bar with 'Diagnostics' highlighted in a red box. Below this, a 'Diagnoses Browser' window is open, showing a tree view on the left with folders for 'Default project', 'Default study', and three 'family' sub-items (fam1, fam2, fam3). The main area shows a list of diagnoses with columns for status, team name, and timestamp. The statuses include 'Running', 'Ready', and 'Error'. A red arrow points from the text 'If you select a specific Diagnoses...' to a specific 'TEAM Diagnosis' entry in the list.

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

Results: Overview

Overview

Diagnostic

Secondary Findings

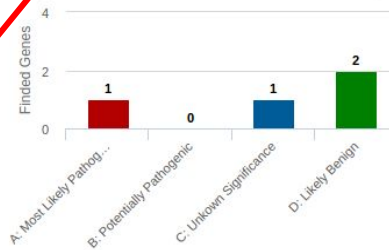
Report

TEAM Diagnosis_3_Fanconi_anemia

New Diagnosis

Total Variants: 5
Diagnostic Variants: 1
Secondary Variants: 4

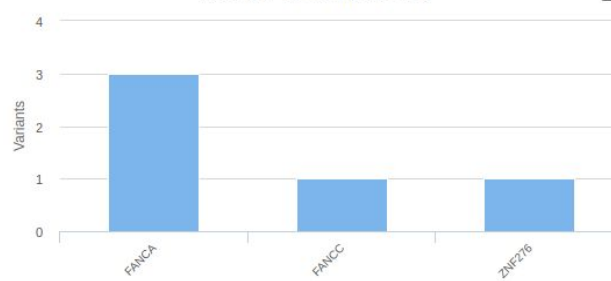
Static Filters



Download Diagnostic ...

Download Secondary ...

Number of Variants/GEN



Number of Variants/Consequence Type

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

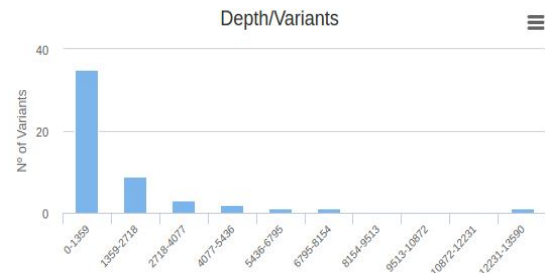
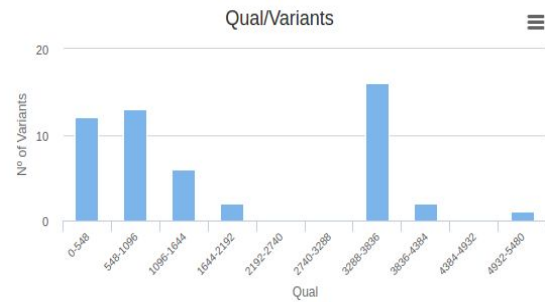
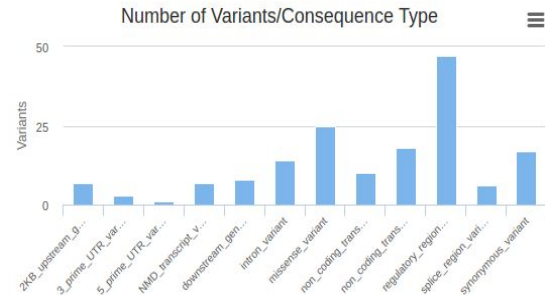
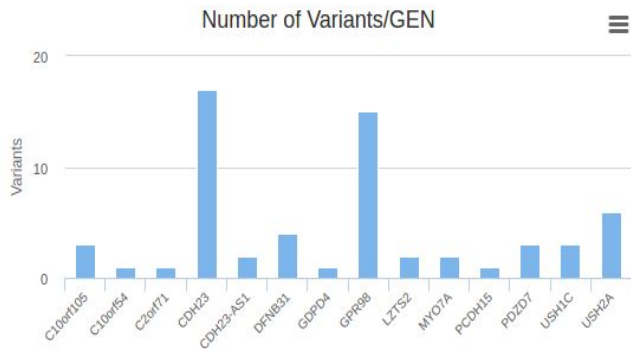
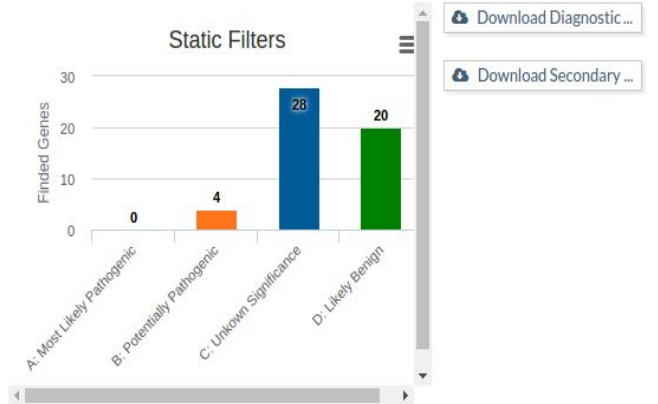
TEAM Diagnosis_RP_905_Usher

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

Variant Data

Overview Comments Frequencies Genome Viewer

X:38240670:C:T

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 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

Variant Data

Overview Comments Frequencies Genome Viewer

Min - Max 101 13:32913005-32913105 Go! << > >>

Detailed information Window size: 101 nts

32913005

Sequence - v ^

ACCTTCCAGGGACAAACC GAACGTGATGAAAAGATCAAAGAACTACTCTATTGGGTTTTTCATACAGCTAGCGGGAAAAAAGTTAAAATTGCAAAG

Gene - v ^

Thr Phe Gln Gly Gln Pro Glu Arg Asp Glu Lys Ile Lys Glu Pro Thr Leu Leu Gly Phe His Thr Ala Ser Gly Lys Lys Val Lys Ile Ala Lys

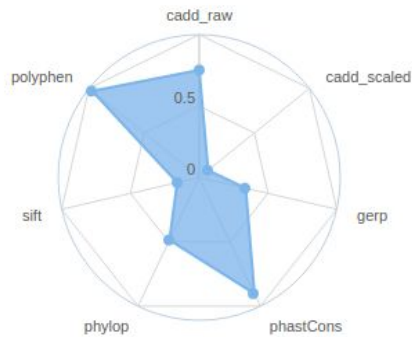
SNP - v ^

rs80358682 rs80358683 rs80358684 rs397507725 COSM13844 rs370723514 rs56386506 rs202022822 rs28897728 C1021892 rs80358694 rs66752726 rs56283738 COSM946805 CD013137 CD076756CD063457 rs206075 rs397507336 rs80359788 rs386833397

Variant Data

Overview Comments Frequencies Genome Viewer

X:38240670:C:T



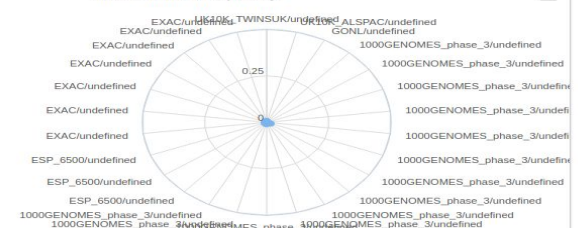
Variant Data

Overview Comments Frequencies Genome Viewer

Study	Population	SuperPopulation	Ref. Allele	Alt. Allele	Ref. Allele Fr.	Alt. Allele Fr.	MAF	O/O	O/1	1/1
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

Page 1 of 3 1 - 10 of 26

Minor Allele Frequency



Results: Secondary Findings

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

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	Polyp...	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

- 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

The screenshot shows the 'Variant Filters' panel with a 'Custom Filters' tab selected. A list of filters is displayed, including Position, Population Freqs., Genotype, Quality, Protein Substitution Scores, Conservation, and Consequence Type. A red arrow points to the 'Custom Filters' tab, and another red arrow points to the 'Search' button.

You can see filters used previously in Filters History

The screenshot shows the 'Filters History' dialog box, which is a table listing previously used filters. The table has columns for Date, Name, and Found. A red arrow points to the 'Clear' button at the top of the dialog.

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=hets AND MAF 1000GP3 < 0.025	1
20/7 16:13	Chromosomal Location: (13) AND Genes: (BRCA2) ...	5

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

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

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

The report can be downloaded as PDF

The screenshot shows a web-based diagnostic report interface. At the top, there are tabs for 'Overview', 'Diagnostic', 'Secondary Findings', and 'Report'. The 'Report' tab is active. On the left side, there is a 'Select to Show' panel with a list of sections and their status (checked or unchecked). Below this panel are three buttons: 'Save report', 'Export report to PDF/Print', and 'Export panel to PDF/Print'. Red arrows point from the text annotations to these buttons. The main report area is titled 'Team report' and includes the following information:

- Job name: TEAM Diagnosis_3_Fanconi_anemia
- Job description: New Diagnosis
- Patient data section with fields for Patient ID (1234), Instrument (Illumina), Analyzed by (test), Sample Origin, Patient Suspected Diagnosis (b), and Patient Diagnosis (Fanconi anemia, complementation group q).
- Generic data section showing Total Variants: 5, Diagnostic Variants: 1, and Secondary Variants: 4.
- Static filter resume section showing Variants found with static filters: A: Most Likely Pathogenic: 1, B: Potentially Pathogenic: 0, C: Unkown Significance: 1, D: Likely Benign: 2.
- Static filters description: A: Most Likely Pathogenic: Sift least than 0.05 and Polyphen bigger than 0.95.

A large red arrow points to the 'Patient Diagnosis' dropdown menu, which is labeled 'Confirmed diagnosis'.

Who is using TEAM?

ciberer isciiii

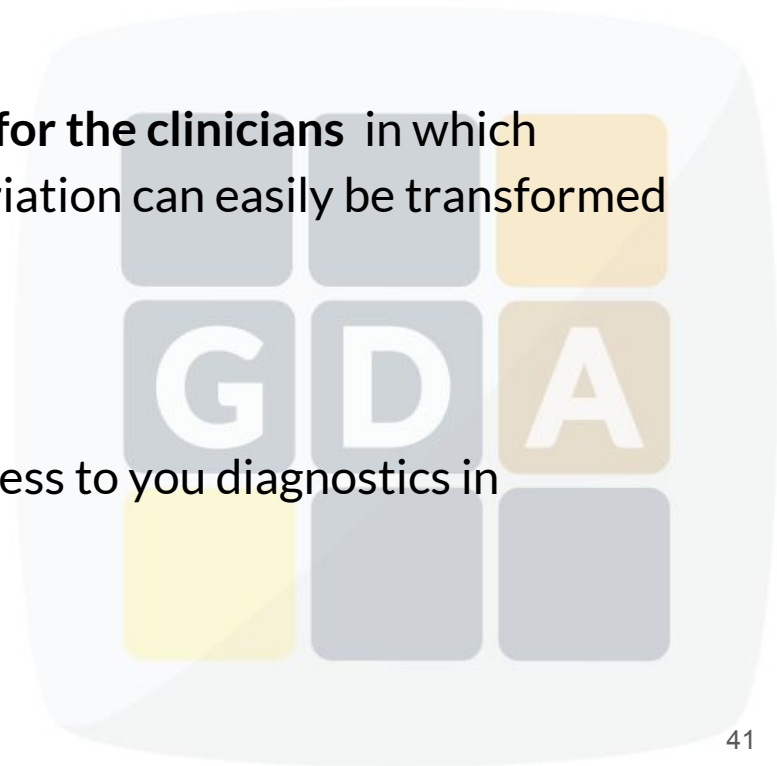
Centro de Investigación Biomédica en Red
Enfermedades Raras

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^{1,2}, Francisco Garcia-Garcia¹, 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

