CANCER GENOMICS CONSORTIUM

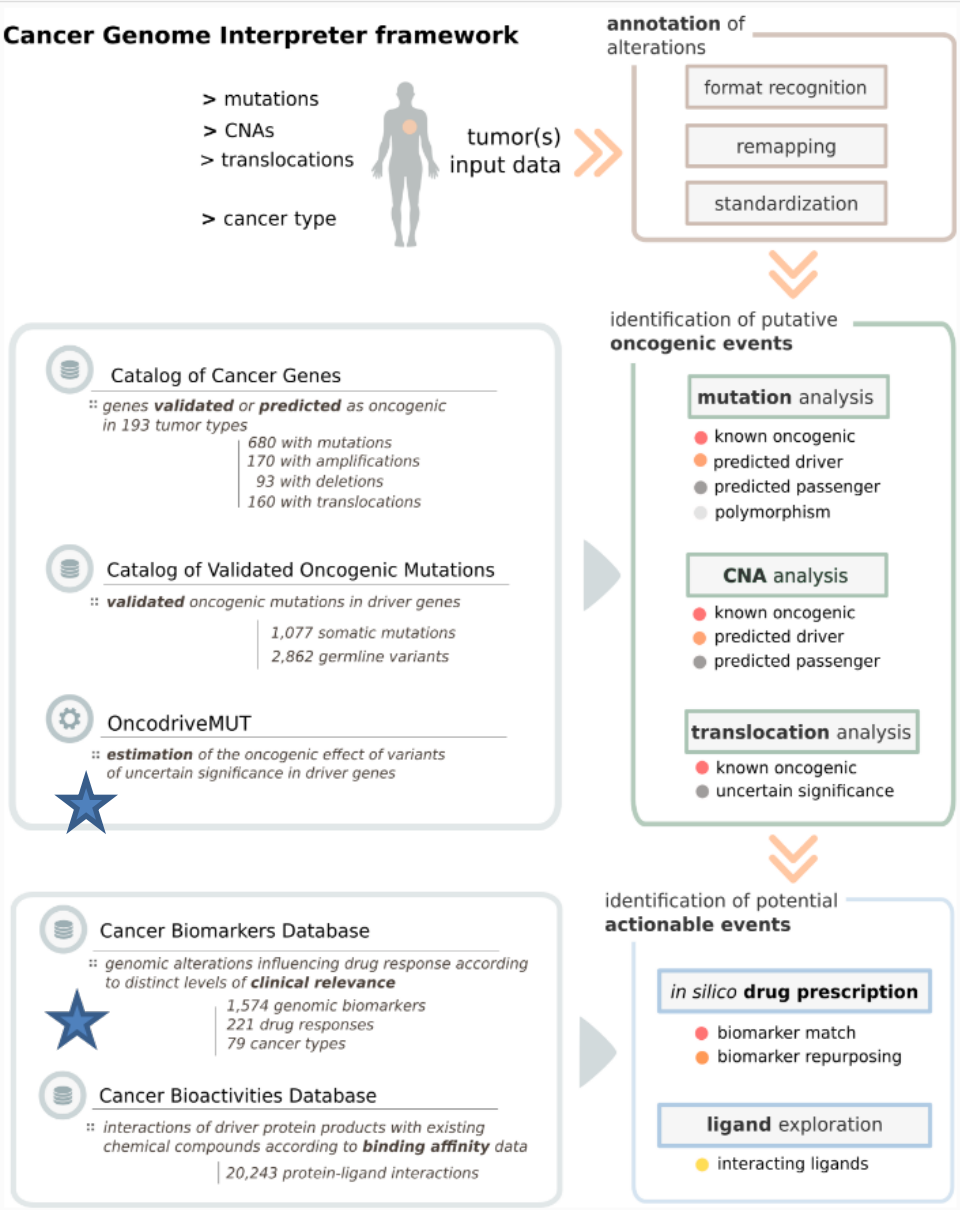
Educating for Best Practices in Clinical Cancer Genomics

CANCER GENOME INTERPRETER

Cancer Genome Interpreter (CGI)

https://www.cancergenomeinterpreter.org/home

CANCER GENOME INTERPRETER

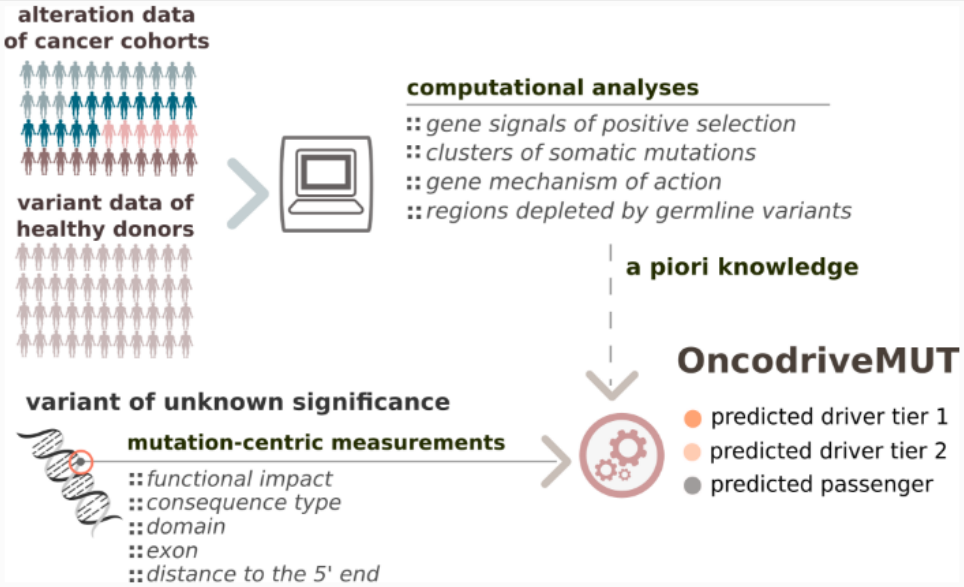


Schema summarizing the CGI framework

Stars indicate additional information in upcoming slides

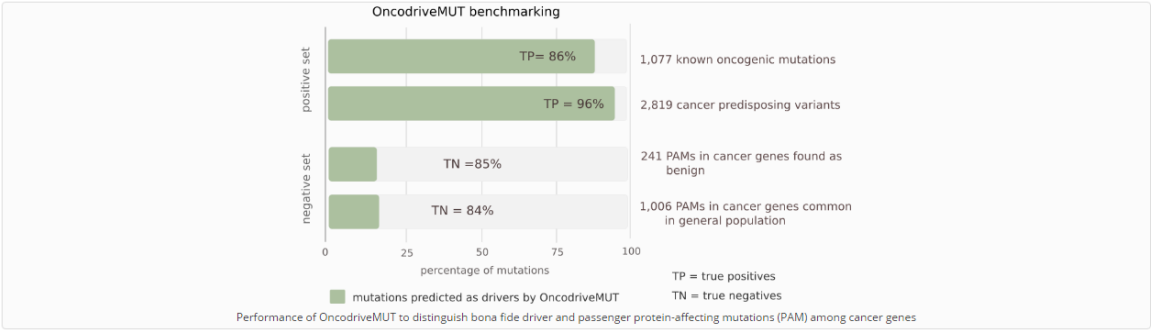
OncodriveMUT

CANCER GENOME INTERPRETER



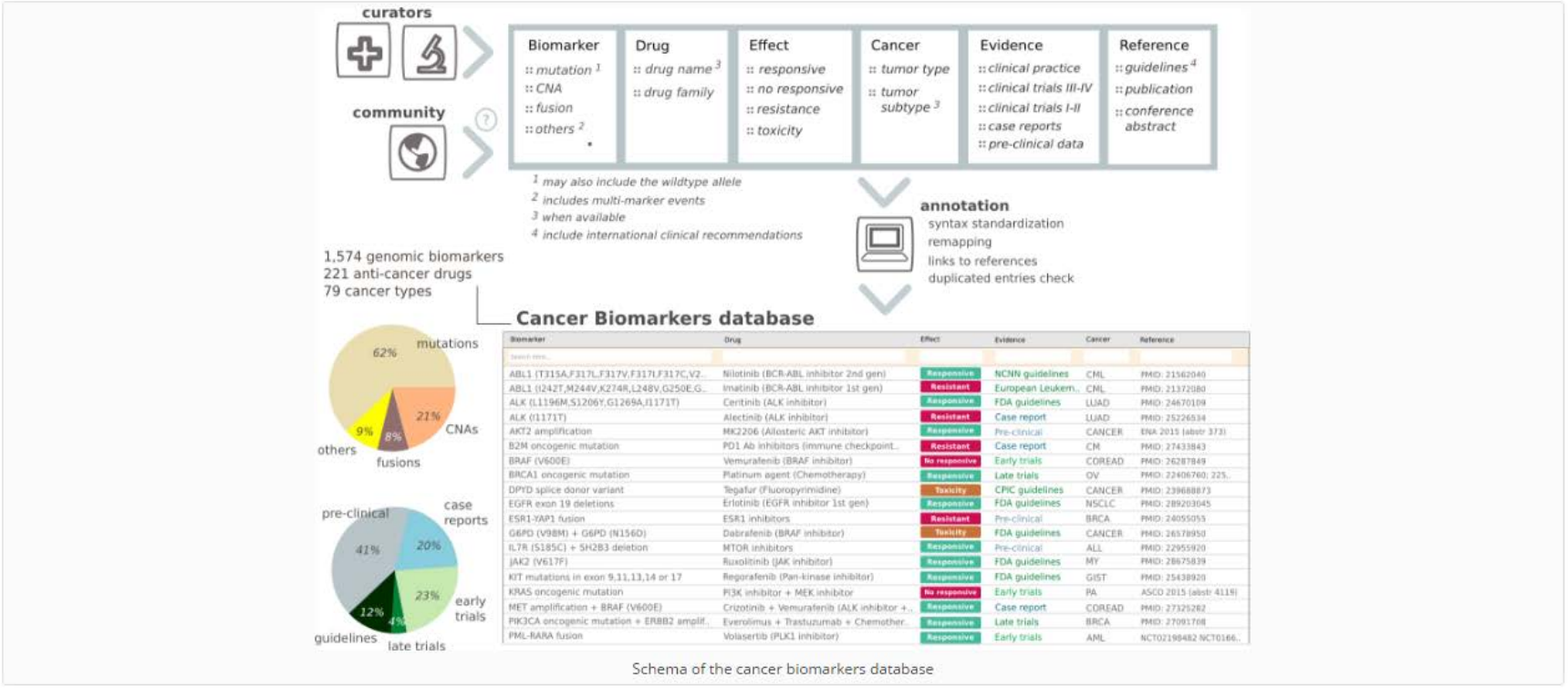
Schema summarizing the OncodriveMUT method framework

Identifies potential driver mutations based on prevalence in disease population, computational analyses, prior knowledge of gene, and mutation-centric measurements.



Performance of OncodriveMUT to distinguish bona fide driver and passenger protein-affecting mutations (PAM) among cancer genes

Cancer Biomarkers Database



Schema of the cancer biomarkers database

Cancer Biomarkers Database is currently curated and maintained under the European Union's Horizon 2020 funding and part of the collaborative effort Global Alliance for Genomics and Health (GA4GH)

Home Page

CANCER GENOME INTERPRETER

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CANCER GENOME INTERPRETER

HOME RESULTS DATASETS FAQ

Login

Cancer Genome Interpreter is designed to support the identification of tumor alterations that drive the disease and detect those that may be therapeutically actionable. CGI relies on existing knowledge collected from several resources and on computational methods that annotate the alterations in a tumor according to distinct levels of evidence.

With a list of genomic alterations and the cancer type as input, the CGI identifies validated driver alterations and annotates and classifies the remaining variants of unknown significance. Then, alterations that are biomarkers of drug response or interact with existing chemical compounds are identified according to current knowledge.

Alterations

Click to see required format

View CGI example results

Add file +

```
Insert one mutation per line, use the same format for all the mutations.

BRAF:V600E              (protein change format, gene symbol)
NM_005157:p.T315I       (protein change format, RefSeq/Ensembl transcript)
chr3:g.178936091G>A     (nucleotide change format, HGVS)
chr17 7578412 A G       (nucleotide change format, GTF)
ERBB2:AMP               (copy number alteration, gene amplification)
TP53:DEL                (copy number alteration, gene deletion)
PML__RARA               (translocation)
```

Cancer type

Search

- (CANCER) Any cancer type
  - (HEMATO) Hematologic malignancies
  - (SOLID) Solid tumors

Run

Disclaimer This resource is intended for research purposes and it must not substitute a doctor's medical judgement or healthcare professional advice.

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- Legal advice
- REST API

CancerGenomeInterpreter

Curated Tweets by @bbglab

bbglab @bbglab

#cancergenomeinterpreter framework now implemented by a REST API cancergenomeinterpreter.org/rest_api

27 Apr

bbglab @bbglab

#cancergenomeinterpreter will be presented today at #AACR17 educational session on "Interpretation of Cancer Genomic Variants" @nlbigas

01 Apr

bbglab @bbglab

Nuria today presented #cancergenomeinterpreter and other @bbglab results to #MIP17 @EACRnews meeting in Amsterdam

16 Mar

David Tamborero @DavidTamborero

#CancerGenomeInterpreter cited as a resource for Implementing Genome-Driven Oncology in @CellCellPressL perspective bit.ly/2koy3QQ

Implementing Genome-Dri...
The era of precision oncolo...
cell.com

13 Feb

Charles Ferté @charles_ferte

#CancerGenomeInterpreter = free online tool to assess Variants Unknown Significance seems awesome Dr Tamborero @IRBBarcelona

Required Mutation Input Format – Follows HGVS Protein Change Format

- Missense:
  - NM_005157:p.T315I
- Stop:
  - TSC2:p.Q1178*
- In-frame insertion:
  - ENST00000326724:p.P1331_A1332insTP
- In-frame deletion:
  - TP53:p.I254_T256delIIT
  - TP53:p.I254_T256del3
  - TP53:p.I254_T256del
- Frameshift
  - APC:p.I1557fs*30
    - The longitude of the frameshift (till the new reading frame ends in a stop codon) needs to be stated to retrieve the corresponding nucleotide change, which is used to calculate certain metrics used by the CGI; if not available, APC:p.I1557fs is also allowed)

Mutation Input Format: Nucleotide Changes

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HGVS = green

Genomic tabular format = orange

Either format is acceptable

- Point mutations:
  - chr3:g.178936091G>A
  - chr17 7578412 A G
- Block substitution:
  - chr3:g.41266066TG>AA
    chr3:g.41266066_41266067delinsAA
  - chr11 533873 CT AC
- Insertions:
  - chr5:g.170837546_170837547insCTGT
    chr5:g.170837545C>CTCTG
  - chr17 37881002 G GGGCTCCCCA
    chr17 37881003 - GGCTCCCCA
- Duplications:
  - chr3:g.30732988_30732989dupTG
    chr3:g.30732988_30732989delinsTGTG
    chr3:30732989_30732990insTG
- Deletions:
  - chr2:g.234183368_234183372delACTCA
    chr2:g.234183368_234183372del
    chr2:g.234183368_234183372del5
  - chr17 37880218 GTTGAGGGAAAACACA G
    chr17 37880219 TTGAGGGAAAACACA -
- Complex indels:
  - chr10:g.52595929_52595931delGGGinsTA
    chr10:g.52595929_52595931delinsTA
  - chr7 140453155 CA TCC

Mutation Input Format: Copy Number Alterations (CNAs) and Translocations

- Amplification:
  - ERBB2:amp
- Deletion
  - TP53:del
- Translocation
  - BCR__ABL1 (equivalent to ABL1__BCR)
    - Two underscores in this instance

Mutation Input Format: Uploaded Files

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- VCF files (in hg19) or text files can be uploaded into CGI
  - See column title specifications on the website by clicking the '?' next to alterations

Selecting the Appropriate Cancer Type

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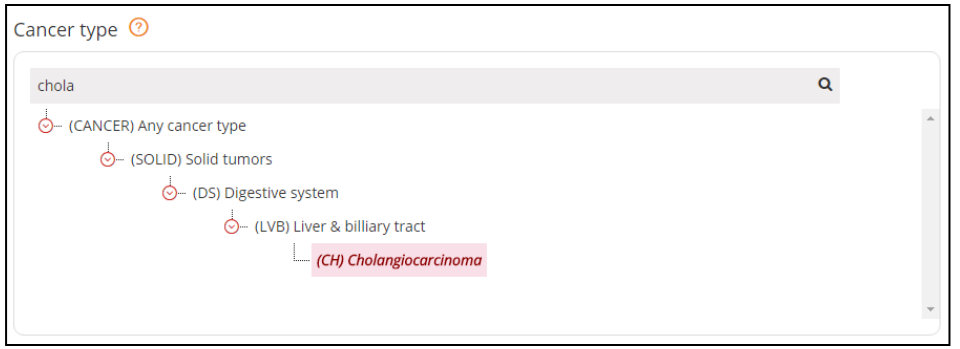
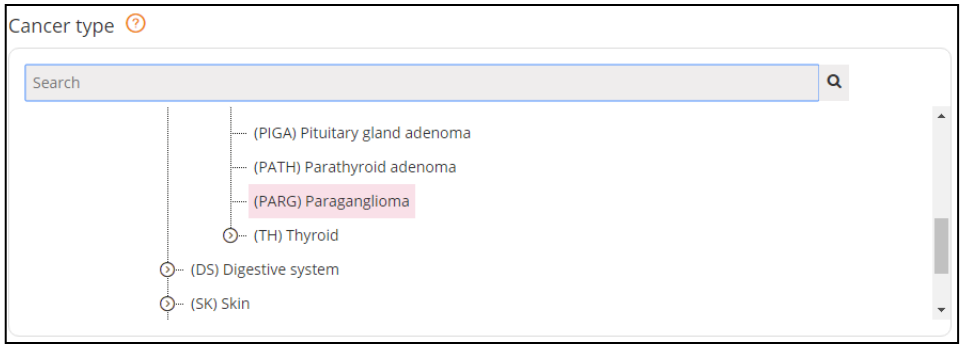
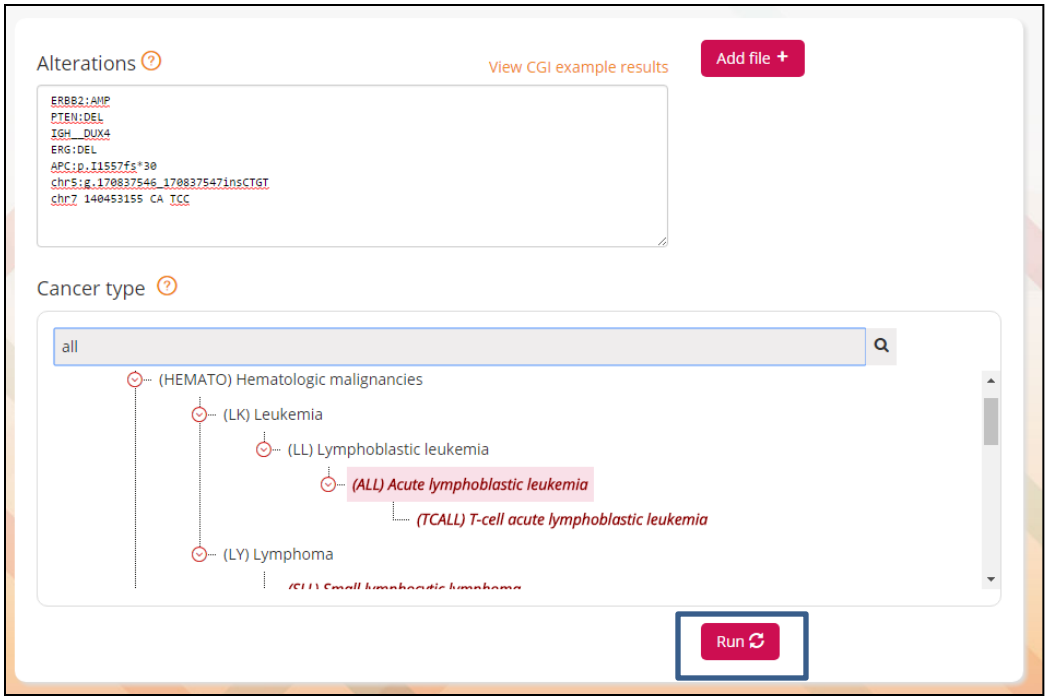
- Enter cancer type manually into search bar
- Search through disease ontology tree
- Click to select cancer type and mark pink.
- If disease is not on the list, that means that no specific information for that cancer type resides in CGI
- Some classification of cancer type (even if it is generic) needs to be selected in order to search





Running a Query

- Input Mutations
  - Manually or Add File
- Select Cancer Type
- Click “Run”
- Allow analysis to Run.
  - If you see an error, check your mutation input format
  - Analysis may take several minutes



Results (Normal View)

CANCER GENOME INTERPRETER

- Tab for alterations has sub-tabs
  - Mutations
  - CNAs
  - Translocations
- Can choose to display all data or only abnormalities that are oncogenic or driver mutations

Mutations

Sample Id	Gene	Protein change	Consequence	Domain	*Oncogenic classification*
Search here...					
default_id	NPM1	p.W288Sfs*12	Frameshift		known in: AML
default_id	APC	p.I1557fs*30	Frameshift		predicted driver: tier 1
default_id	BRAF	p.D594Efs*18	Frameshift	Pkinase_Tyr	predicted driver: tier 2

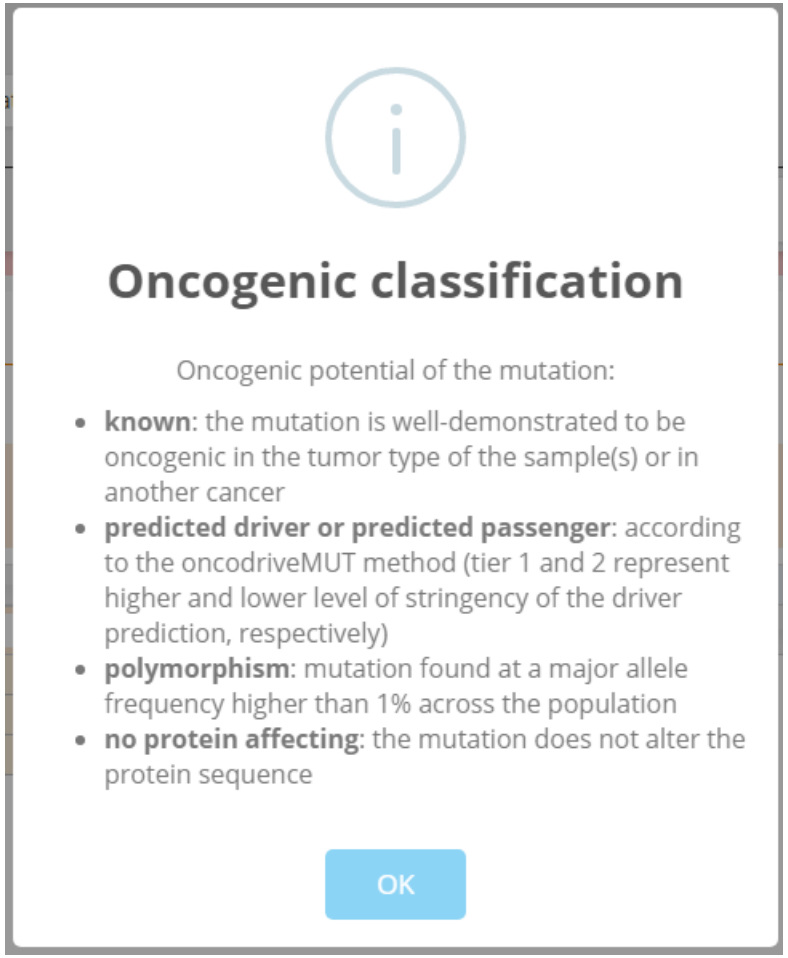
CNAs

Sample Id	Gene	Cna	*Oncogenic classification*
Search here...			
tcgi	ERBB2	AMP	known in: BRCA;OV;NSCLC;ST;B...
tcgi	PTEN	DEL	known in: G;PRAD;ED;BRCA;OV;...
tcgi	ERG	DEL	predicted passenger

Translocations

Sample Id	Gene translocation	*Oncogenic classification*
Search here...		
tcgi	DUX4__IGH	uncertain relevance

Oncogenic Classifications



This pop-up displays when the '?' next to "Oncogenic classification" is clicked.

Advanced View of Results: Mutations

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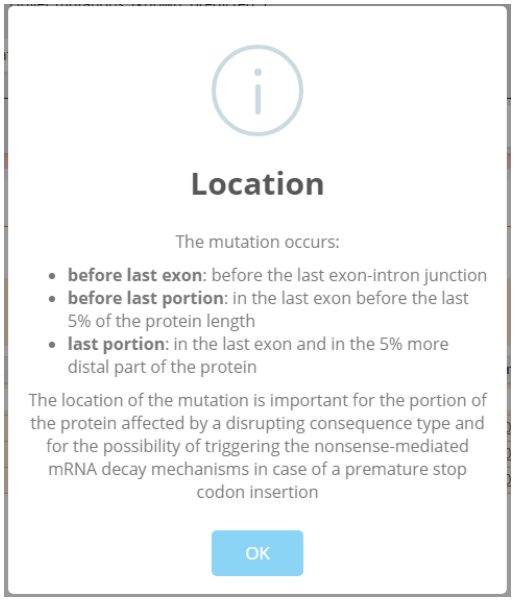
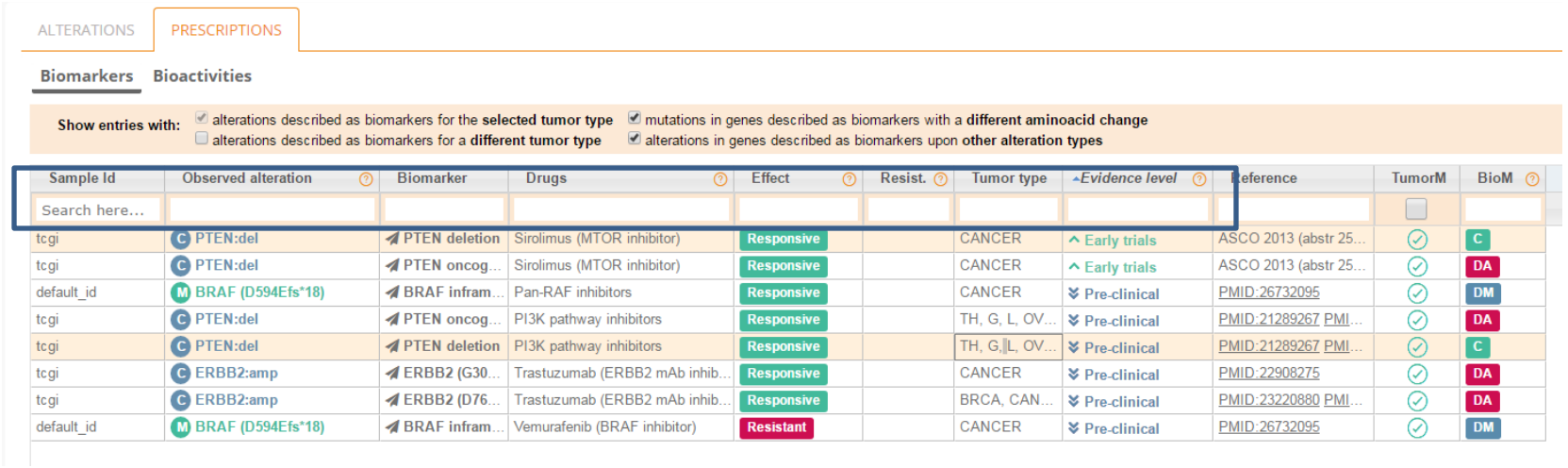
- Adds the following information to your results tables:
  - Mutations
    - GDNA
    - Transcript
    - Exon
    - Location in relation to last exon of gene (right)
    - Tumor Driver according to CGI group publication (PMID:25759023) – hover over to specify if the gene is a driver in this tumor type or other tumor types.
    - Role – mechanism of action (OG, TSG, ambiguous)
    - In Cluster – does this mutation fall within more commonly mutated regions in that gene.



Therapeutic Information

CANCER GENOME INTERPRETER

- Biomarkers



ALTERATIONS | PRESCRIPTIONS

Biomarkers | Bioactivities

Show entries with:
- alterations described as biomarkers for the **selected tumor type**
- alterations described as biomarkers for a **different tumor type**
- mutations in genes described as biomarkers with a **different aminoacid change**
- alterations in genes described as biomarkers upon **other alteration types**

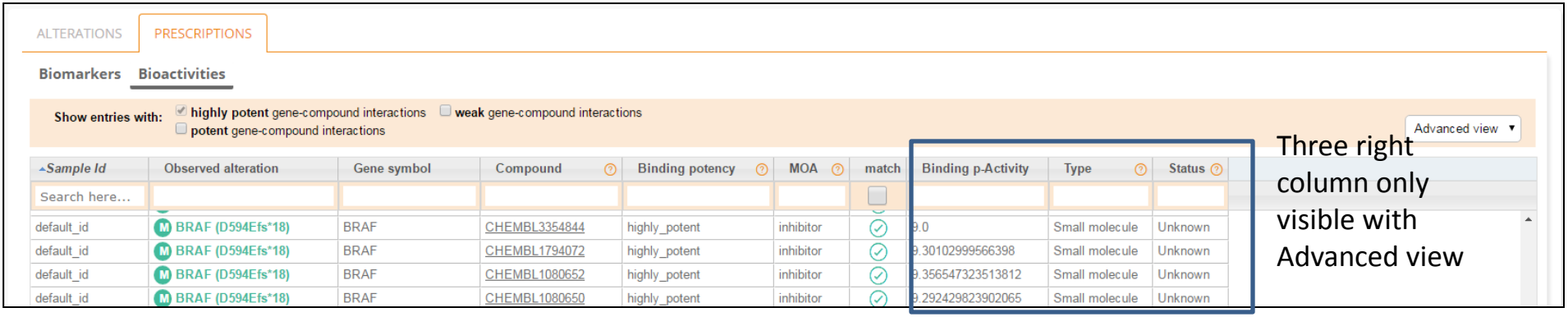
Sample Id	Observed alteration	Biomarker	Drugs	Effect	Resist.	Tumor type	Evidence level	Reference	TumorM	BioM
Search here...										
tcgi	C PTEN:del	PTEN deletion	Sirolimus (MTOR inhibitor)	Responsive		CANCER	Early trials	ASCO 2013 (abstr 25...	✓	C
tcgi	C PTEN:del	PTEN oncog...	Sirolimus (MTOR inhibitor)	Responsive		CANCER	Early trials	ASCO 2013 (abstr 25...	✓	DA
default_id	M BRAF (D594Efs*18)	BRAF inframe...	Pan-RAF inhibitors	Responsive		CANCER	Pre-clinical	PMID:26732095	✓	DM
tcgi	C PTEN:del	PTEN oncog...	PI3K pathway inhibitors	Responsive		TH, G, L, OV...	Pre-clinical	PMID:21289267 PMI...	✓	DA
tcgi	C PTEN:del	PTEN deletion	PI3K pathway inhibitors	Responsive		TH, G, L, OV...	Pre-clinical	PMID:21289267 PMI...	✓	C
tcgi	C ERBB2:amp	ERBB2 (G30...	Trastuzumab (ERBB2 mAb inhib...	Responsive		CANCER	Pre-clinical	PMID:22908275	✓	DA
tcgi	C ERBB2:amp	ERBB2 (D76...	Trastuzumab (ERBB2 mAb inhib...	Responsive		BRCA, CAN...	Pre-clinical	PMID:23220880 PMI...	✓	DA
default_id	M BRAF (D594Efs*18)	BRAF inframe...	Vemurafenib (BRAF inhibitor)	Resistant		CANCER	Pre-clinical	PMID:26732095	✓	DM

- Effect – Responsive, No responsive, Resistant, Increased toxicity
- Resist. – Indicates any additional alterations that would confer resistance to the therapy
- Evidence level – Different from approval status; Early trials (phase I & II), Late trials (phase III, IV), pre-clinical, Clinical
- Reference – indicates reference, may include links to PubMed
- TumorM – checked if the tumor type matches a tumor type in which the biomarker has been observed
- BioM – indicates match between alteration and the observed biomarker; C = complete match, DM = different mutation (different amino acid change), DA = different alteration (biomarker is not a mutation)

Therapeutic Information

CANCER GENOME INTERPRETER

- Bioactivities



- Compound – ChEMBL compound ID and link to ChEMBL Compound report card
- Binding potency – Highly Potent = >9 (1nM); Potent = >6 (1uM); Weak = >3 (1mM)
  - See Binding p-Activity
- MOA – mechanism of action
- Match – Checked when mechanism of action coincides with role of gene in cancer
- Type – molecular type of compound: oligonucleotide, oligosaccharide, protein, small molecule, unknown
- Status – status of clinical approval of compound: Approved, early clinical trials, late clinical trials, pre-clinical, unknown

Archiving/Saving Results

- Can Download results in zipped folder.
  - No Log in needed
- Can Share results via email as well
- To save your analysis, you will need to log into your account
  - Can log in with Google account

Other Available Downloads

- Select Datasets from top banner
- Zipped folder available for download for the following
  - Cancer Genes
  - Validated Oncogenic Mutations
  - Cancer Biomarkers
  - Cancer Bioactivities

CANCER GENOME INTERPRETER

Scenario #1

- You want to make a Pan Cancer gene list from the Cancer Genome Interpreter datasets.
  - Download TSV files and sort to make Cancer list

Making a Pan Cancer List from CGI

- Click on “Datasets” on top banner.
  - Select “Cancer Genes” tab.
    - Click “Download”
    - Save files from downloaded folder
    - Open gene_MoA.tsv (mechanism of action)
      - All genes are listed alphabetically and categorized as Act (activating mutation/alteration), LOF (loss of function), or ambiguous.

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Scenario #2

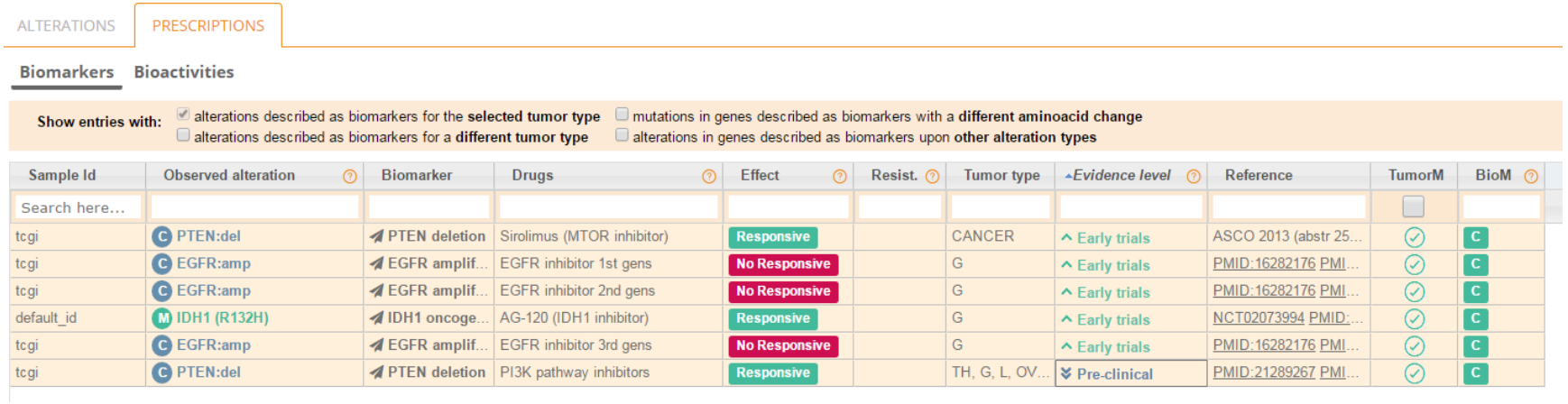
- You have a complex abnormal NGS panel you would like interpreted. Which abnormalities are targetable?
  - PTEN deletion
  - IDH1:R132H
  - EGFR amplification
  - CIC: R215W
  - PRKDC frameshift deletion

Converting mutations to correct input format (See slides 6-9)

- PTEN:del
- IDH1:p.R132H
- EGFR:amp
- CIC:p.R215W
- PRKDC:p.1351fs

- Select ‘Glioma’ for cancer type

Results – Go to Prescriptions



ALTERATIONS | PRESCRIPTIONS

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tcgi	C EGFR:amp	EGFR amplif...	EGFR inhibitor 1st gens	No Responsive		G	Early trials	PMID:16282176 PMI...	✓	C
tcgi	C EGFR:amp	EGFR amplif...	EGFR inhibitor 2nd gens	No Responsive		G	Early trials	PMID:16282176 PMI...	✓	C
default_id	M IDH1 (R132H)	IDH1 oncoge...	AG-120 (IDH1 inhibitor)	Responsive		G	Early trials	NCT02073994 PMID:...	✓	C
tcgi	C EGFR:amp	EGFR amplif...	EGFR inhibitor 3rd gens	No Responsive		G	Early trials	PMID:16282176 PMI...	✓	C
tcgi	C PTEN:del	PTEN deletion	PI3K pathway inhibitors	Responsive		TH, G, L, OV...	Pre-clinical	PMID:21289267 PMI...	✓	C

- Drugs for EGFR amplification have “No Responsive” effect.
- Target PTEN deletion with MTOR inhibitor or PI3K pathway inhibitor
- Target IDH1 with IDH1 inhibitor
- Cite references in report if necessary

Scenario #3

- You are building an interface to aid in interpretation and analysis of genomic testing results. You would like to incorporate CGI into your product.
  - Use of API

Shared API

- https://www.cancergenomeinterpreter.org/rest_api
- API is shared online
- Some of the functionality of the API requires log in to account
  - Can sign up with Google account

Education/ Tutorials

- https://www.cancergenomeinterpreter.org/faq#q01

Contacts

- bbglab@irbbarcelona.org – Contact for comments, suggestions, bug reports