



CANCER GENOMICS CONSORTIUM

Educating for Best Practices in Clinical Cancer Genomics

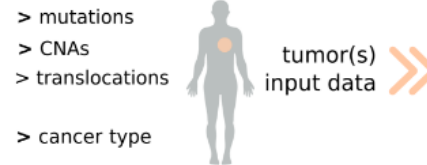


CANCER GENOME
INTERPRETER

Cancer Genome Interpreter (CGI)

[https://www.cancergenomeint
erpreter.org/home](https://www.cancergenomeinterpreter.org/home)

Cancer Genome Interpreter framework



annotation of alterations

format recognition
remapping
standardization

identification of putative oncogenic events

mutation analysis

● known oncogenic
● predicted driver
● predicted passenger
● polymorphism

CNA analysis

● known oncogenic
● predicted driver
● predicted passenger

translocation analysis

● known oncogenic
● uncertain significance

identification of potential actionable events

in silico drug prescription

● biomarker match
● biomarker repurposing

ligand exploration

● interacting ligands



Catalog of Cancer Genes

:: genes **validated** or **predicted** as oncogenic in 193 tumor types

680 with mutations
170 with amplifications
93 with deletions
160 with translocations



Catalog of Validated Oncogenic Mutations

:: **validated** oncogenic mutations in driver genes

1,077 somatic mutations
2,862 germline variants



OncodriveMUT

:: **estimation** of the oncogenic effect of variants of uncertain significance in driver genes



Cancer Biomarkers Database

:: genomic alterations influencing drug response according to distinct levels of **clinical relevance**

1,574 genomic biomarkers
221 drug responses
79 cancer types



Cancer Bioactivities Database

:: interactions of driver protein products with existing chemical compounds according to **binding affinity** data

20,243 protein-ligand interactions

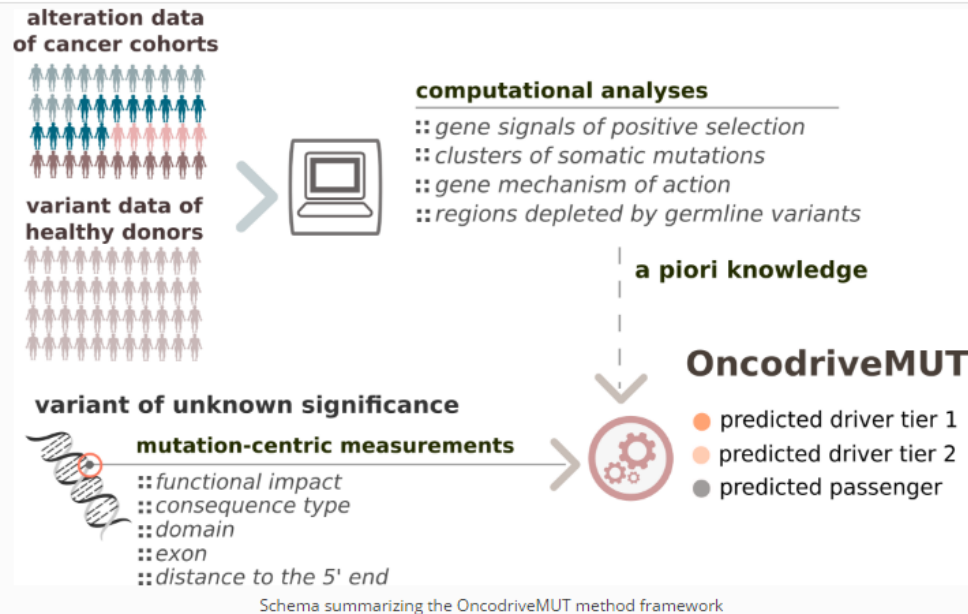
Stars indicate
additional
information in
upcoming slides

Schema summarizing the CGI framework

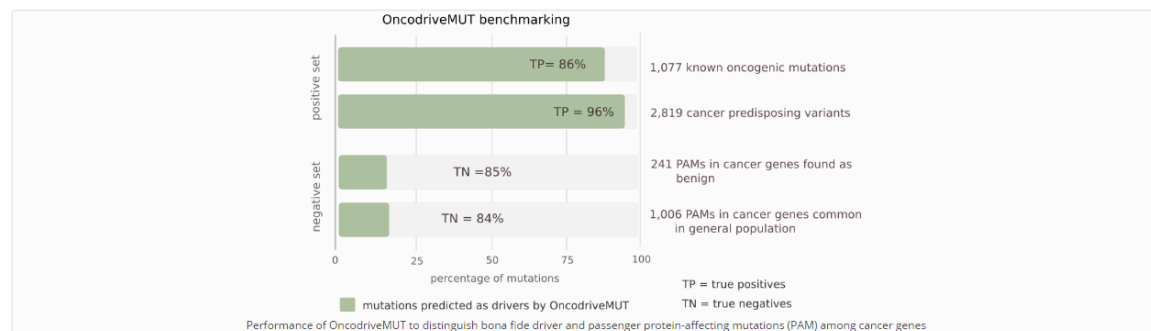
OncodriveMUT



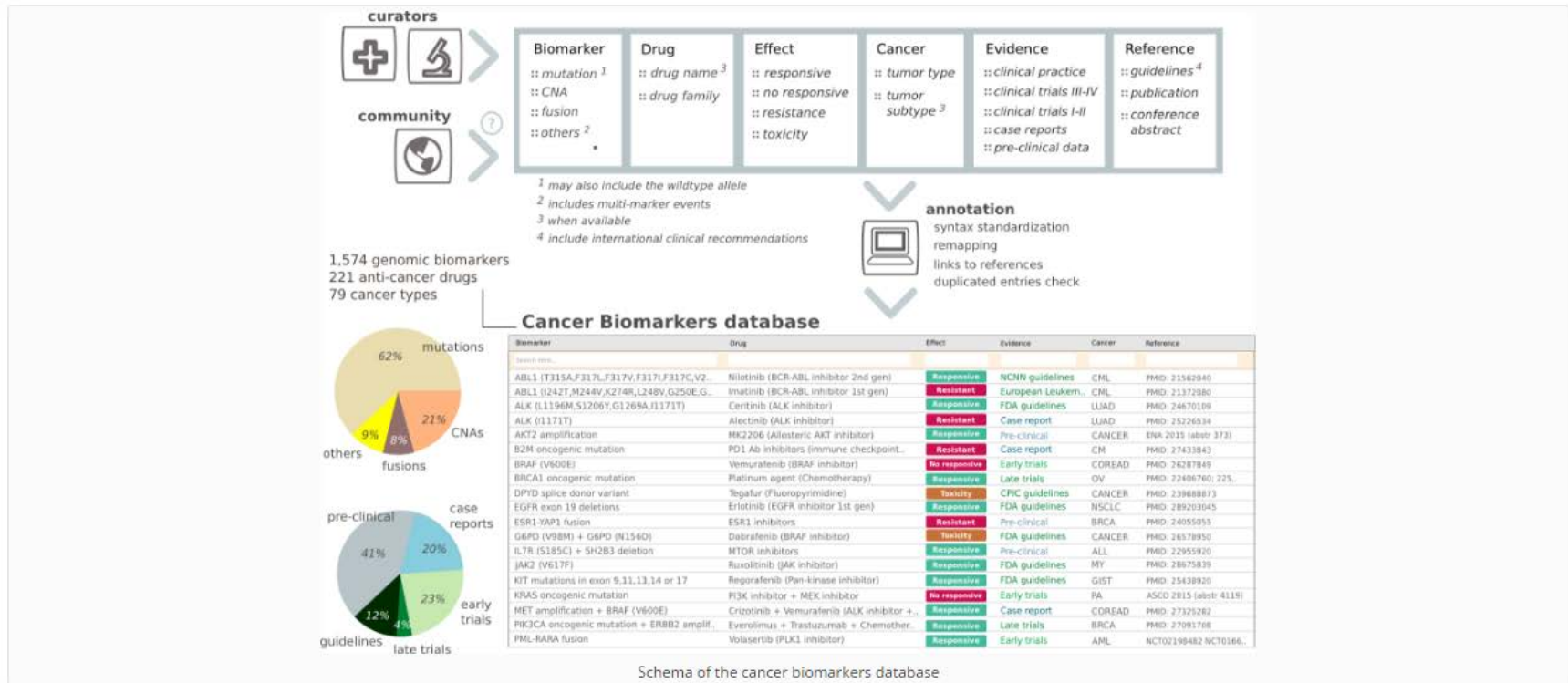
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Identifies potential driver mutations based on prevalence in disease population, computational analyses, prior knowledge of gene, and mutation-centric measurements.



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

This resource is intended for purely research purposes. It should not be used for medical or professional advice. We use cookies to track usage and preferences. [I Understand](#)



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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MedBioinformatics



ICREA

La Marató 

TECNIOspring
Tech transfer
through researchers' mobility



Co-funded by the EU
European Union

ACCIÓ

Generalitat de Catalunya

inB

- 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 #ACR17 educational session on "Interpretation of Cancer Genomic Variants"
@nbigas

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 Ferte**
@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_T256delIII
 - 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

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_41266067delinsA
A
 - chr11 533873 CT AC
- Insertions:
 - chr5:g.170837546_170837547insCT
GT
chr5:g.170837545C>CTCTG
 - chr17 37881002 G
GGGCTCCCCA
chr17 37881003 - GGCTCCCCA
- Duplications:
 - chr3:g.30732988_30732989dupTG
chr3:g.30732988_30732989delinsT
GTG
chr3:30732989_30732990insTG
- Deletions:
 - chr2:g.234183368_234183372delA
CTCA
chr2:g.234183368_234183372del
chr2:g.234183368_234183372del5
 - chr17 37880218
GTTGAGGGAAAACACA G
chr17 37880219
TTGAGGGAAAACACA -
- Complex indels:
 - chr10:g.52595929_52595931delG
GGinsTA
chr10:g.52595929_52595931delins
TA
 - 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



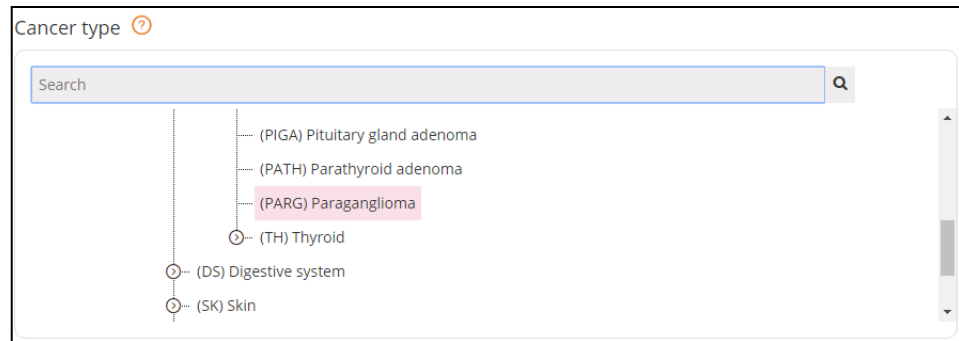
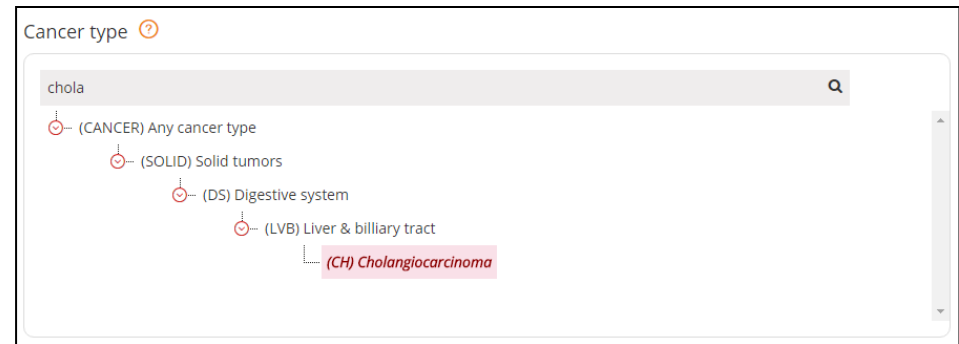
Mutation Input Format: Uploaded Files

- 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



- 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

The screenshot shows the Cancer Genome Interpreter interface. The 'Alterations' section contains a text box with the following mutations: `ERBB2:AMP`, `PTEN:DEL`, `IGH_DUX4`, `ERG:DEL`, `APC:p.I1557fs*30`, `chr5:g.170837546_170837547insCTGT`, and `chr7:140453155 CA TCC`. There is a 'View CGI example results' link and an 'Add file +' button. The 'Cancer type' section has a search bar with 'all' entered. Below the search bar is a hierarchical tree of cancer types: (HEMATO) Hematologic malignancies, (LK) Leukemia, (LL) Lymphoblastic leukemia, (ALL) Acute lymphoblastic leukemia (highlighted in pink), (TCALL) T-cell acute lymphoblastic leukemia, (LY) Lymphoma, and (CLL) Small lymphocytic lymphoma. A 'Run' button with a circular arrow icon is at the bottom right.

Results (Normal View)



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- 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



Oncogenic classification

Oncogenic potential of the mutation:

- **known:** the mutation is well-demonstrated to be oncogenic in the tumor type of the sample(s) or in another cancer
- **predicted driver or predicted passenger:** according to the oncodriveMUT method (tier 1 and 2 represent higher and lower level of stringency of the driver prediction, respectively)
- **polymorphism:** mutation found at a major allele frequency higher than 1% across the population
- **no protein affecting:** the mutation does not alter the protein sequence

OK


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.



Location

The mutation occurs:

- **before last exon:** before the last exon-intron junction
- **before last portion:** in the last exon before the last 5% of the protein length
- **last portion:** in the last exon and in the 5% more distal part of the protein

The location of the mutation is important for the portion of the protein affected by a disrupting consequence type and for the possibility of triggering the nonsense-mediated mRNA decay mechanisms in case of a premature stop codon insertion

OK

Therapeutic Information



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• Biomarkers

ALTERATIONS PRESCRIPTIONS										
Biomarkers Bioactivities										
Show entries with: <input checked="" type="checkbox"/> alterations described as biomarkers for the selected tumor type <input checked="" type="checkbox"/> mutations in genes described as biomarkers with a different amino acid change <input type="checkbox"/> alterations described as biomarkers for a different tumor type <input checked="" type="checkbox"/> 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 infram...	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 infram...	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



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- Bioactivities

ALTERATIONS PRESCRIPTIONS

Biomarkers Bioactivities

Show entries with: ☒ highly potent gene-compound interactions ☐ weak gene-compound interactions
☐ potent gene-compound interactions

Advanced view ▼

Sample Id	Observed alteration	Gene symbol	Compound	Binding potency	MOA	match	Binding p-Activity	Type	Status
Search here...									
default_id	BRAF (D594Efs*18)	BRAF	CHEMBL3354844	highly_potent	inhibitor		9.0	Small molecule	Unknown
default_id	BRAF (D594Efs*18)	BRAF	CHEMBL1794072	highly_potent	inhibitor		9.30102999566398	Small molecule	Unknown
default_id	BRAF (D594Efs*18)	BRAF	CHEMBL1080652	highly_potent	inhibitor		9.356547323513812	Small molecule	Unknown
default_id	BRAF (D594Efs*18)	BRAF	CHEMBL1080650	highly_potent	inhibitor		9.292429823902065	Small molecule	Unknown

Three right
column only
visible with
Advanced view

- 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



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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.



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
Biomarkers

Bioactivities

Show entries with: ☒ alterations described as biomarkers for the **selected tumor type** ☐ mutations in genes described as biomarkers with a **different aminoacid change**
☐ alterations described as biomarkers for a **different tumor type** ☐ 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...									<input type="checkbox"/>	
tcgi	C PTEN:del	PTEN deletion	Sirolimus (MTOR inhibitor)	Responsive		CANCER	Early trials	ASCO 2013 (abstr 25...	<input checked="" type="checkbox"/>	C
tcgi	C EGFR:amp	EGFR amplif...	EGFR inhibitor 1st gens	No Responsive		G	Early trials	PMID:16282176 PMI...	<input checked="" type="checkbox"/>	C
tcgi	C EGFR:amp	EGFR amplif...	EGFR inhibitor 2nd gens	No Responsive		G	Early trials	PMID:16282176 PMI...	<input checked="" type="checkbox"/>	C
default_id	M IDH1 (R132H)	IDH1 oncoge...	AG-120 (IDH1 inhibitor)	Responsive		G	Early trials	NCT02073994 PMID:...	<input checked="" type="checkbox"/>	C
tcgi	C EGFR:amp	EGFR amplif...	EGFR inhibitor 3rd gens	No Responsive		G	Early trials	PMID:16282176 PMI...	<input checked="" type="checkbox"/>	C
tcgi	C PTEN:del	PTEN deletion	PI3K pathway inhibitors	Responsive		TH, G, L, OV...	Pre-clinical	PMID:21289267 PMI...	<input checked="" type="checkbox"/>	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@irbbbarcelona.org – Contact for comments, suggestions, bug reports