Precision medicine: NGS variant analysis and interpretation for translational research

PanDrugs: Matching mutations with therapies

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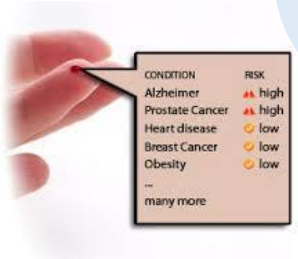
Centro Nacional de Investigaciones Oncológicas

INSTITUTO GULBENKIAN DE CIÊNCIA

Predisposition



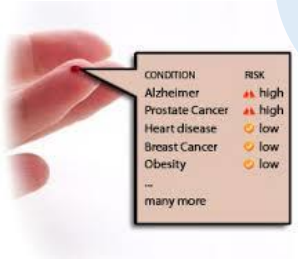
Prognosis

Actionable genomic alterations

Diagnosis

Treatment

Predisposition



Prognosis

Genomic alterations

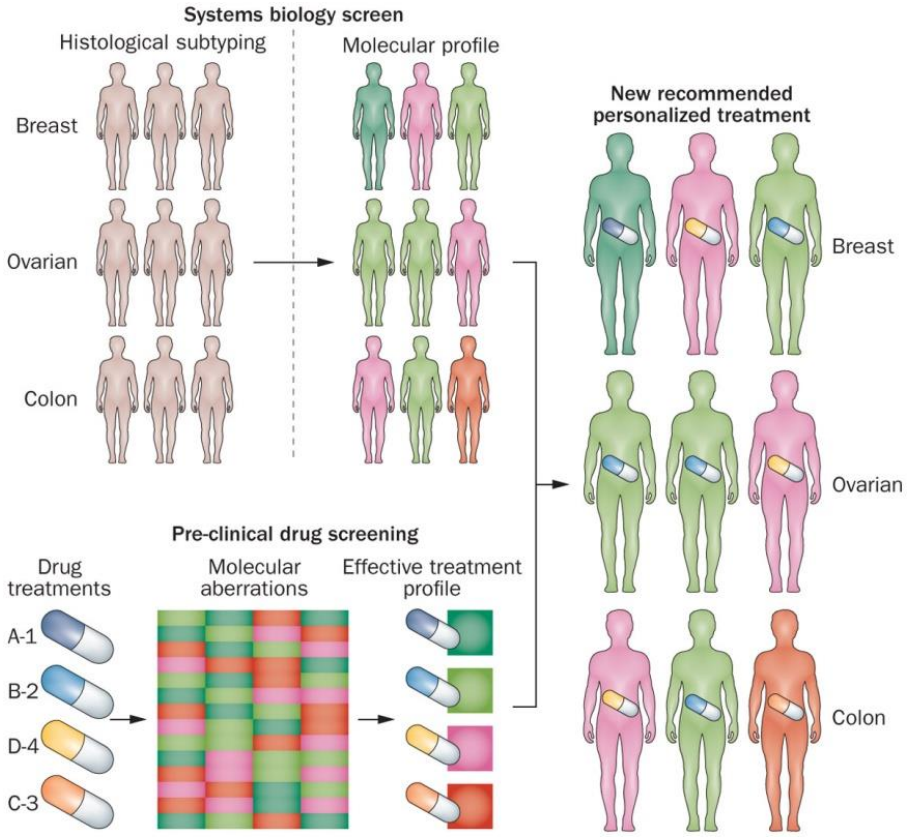
Pharmacogenomics

Diagnosis

Treatment

Pharmacogenomics

Studies the effect of the genomic alterations in the drug response.



- Breaks the rule"one size fits all"
- Individual variation predicts:
  - Response
  - No response
  - Side effects
- Tailors a suitable treatment for a stratified patient

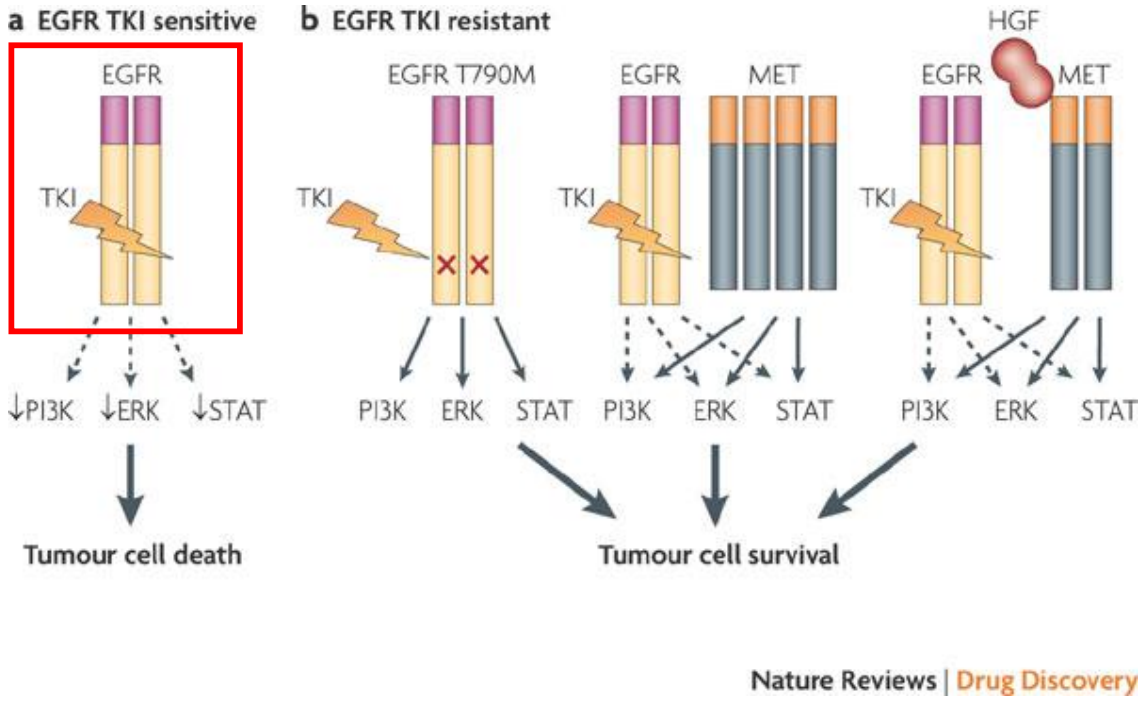
Werner, H. M. J. et al. (2014) Cancer Systems Biology: a peek into the future of patient care?Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2014.6

Gene-drug considerations

- Target/Biomarker

Target & marker genes

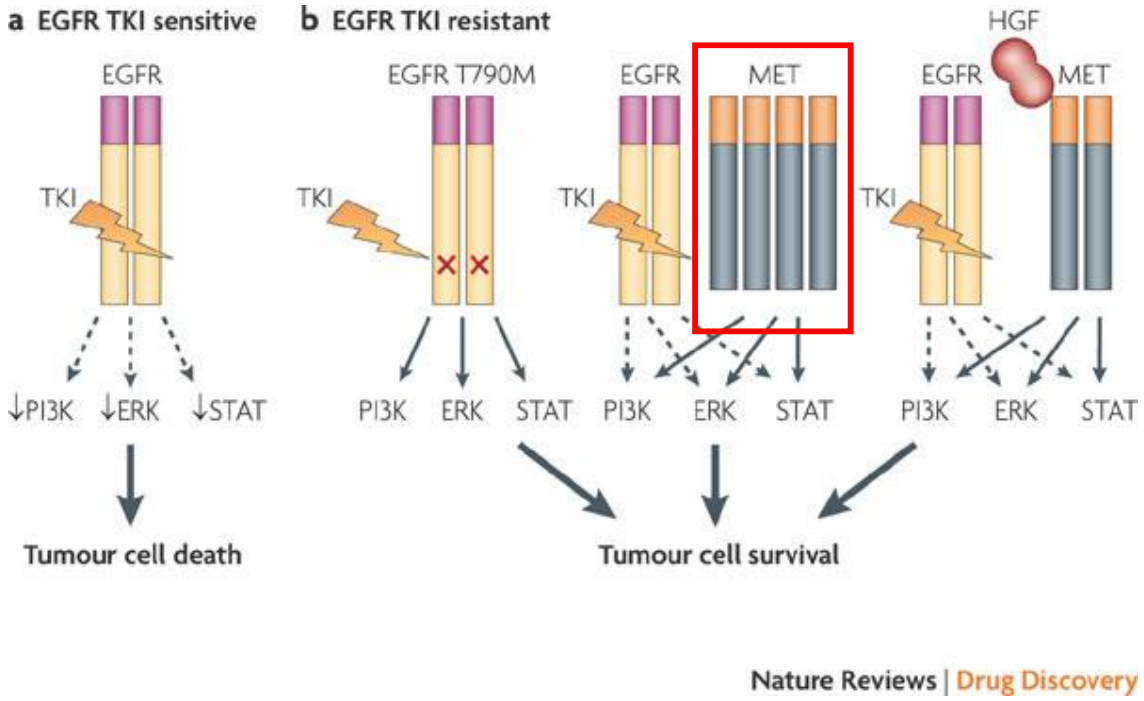
TARGET human gene that **contributes to a disease phenotype and can be targeted directly by a drug (small molecule, monoclonal antibody, …)**



Target & marker genes

TARGET human gene that **contributes to a disease phenotype and can be targeted directly by a drug (small molecule, monoclonal antibody, …)**

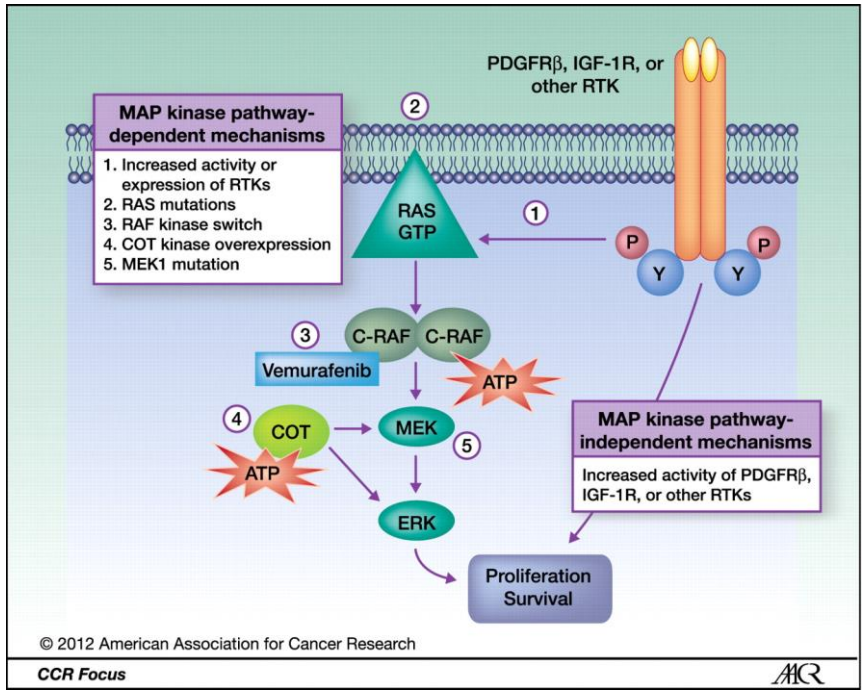
MARKER its **genetic status** is associated with a drug response by **clinical or experimental** evidences



Gene-drug considerations

- Target/Biomarker
- Sensitivity/Resistance

Sensitivity vs Resistance



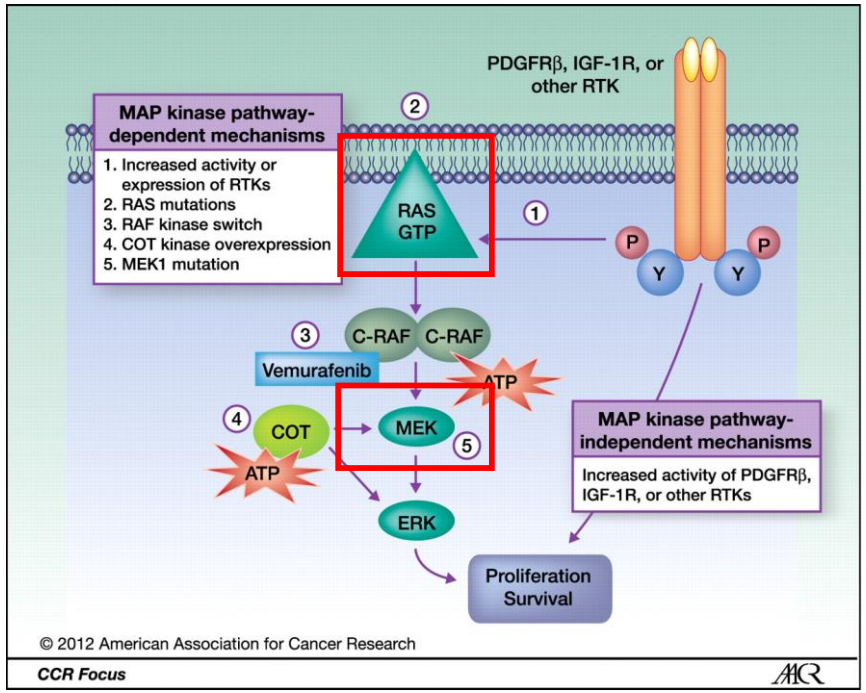
Melanoma treatment with BRAF mutation

VEMURAFENIB

GEMCITABINE

Advanced or metastatic pancreatic cancer

Sensitivity vs Resistance



Melanoma treatment with BRAF mutation

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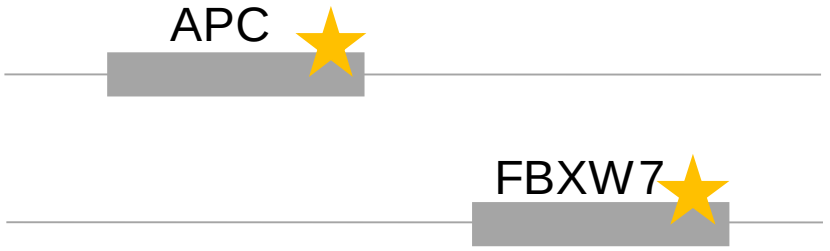
GEM BINE

Advanced or metastatic pancreatic cancer



Gene-drug considerations

- Target/Biomarker
- Sensitivity/Resistance
- Type of event in drug response

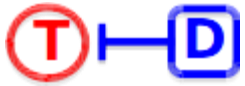
Gene-drug considerations

- Target/Biomarker
- Sensitivity/Resistance
- Type of event in drug response
- Direct/Indirect drug action

Direct/Indirect associations

DRUG-GENE DIRECT ASSOCIATIONS

The altered gene is the target or biomarker of the drug



DRUG-GENE INDIRECT ASSOCIATIONS

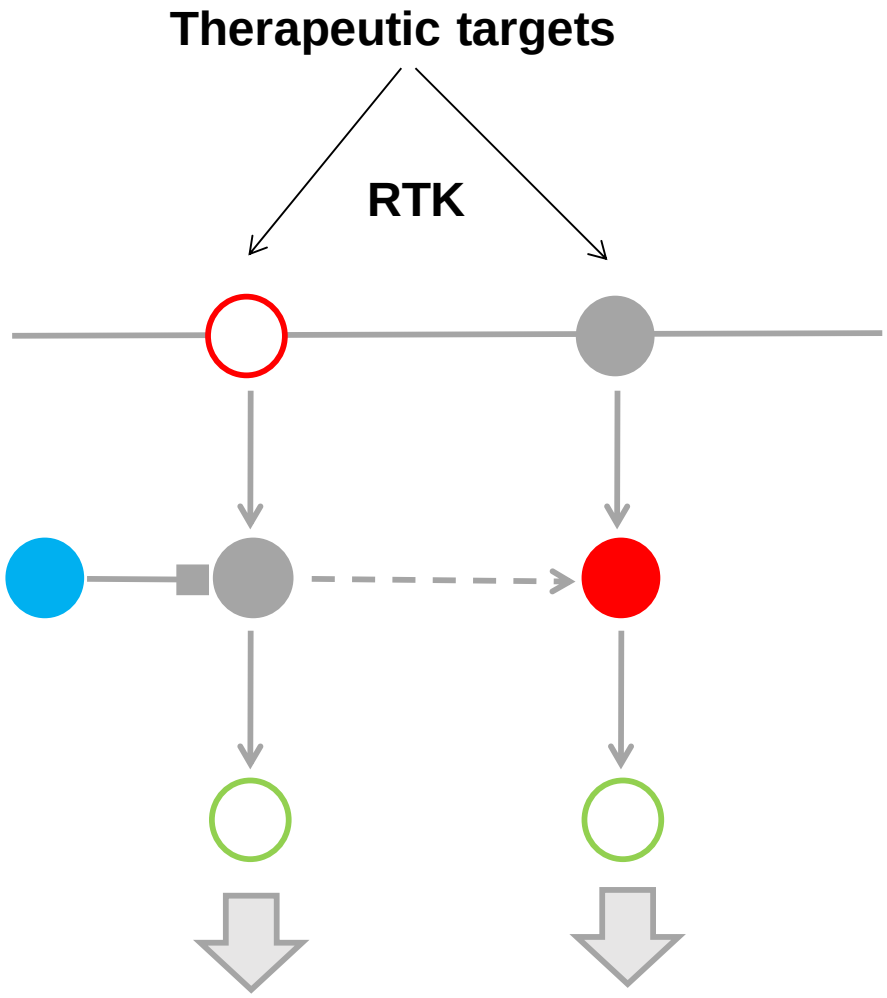
The drug has as a target a gene related to the altered one

D Drug

T Altered target gene

G Altered non target gene

T Wild type target gene



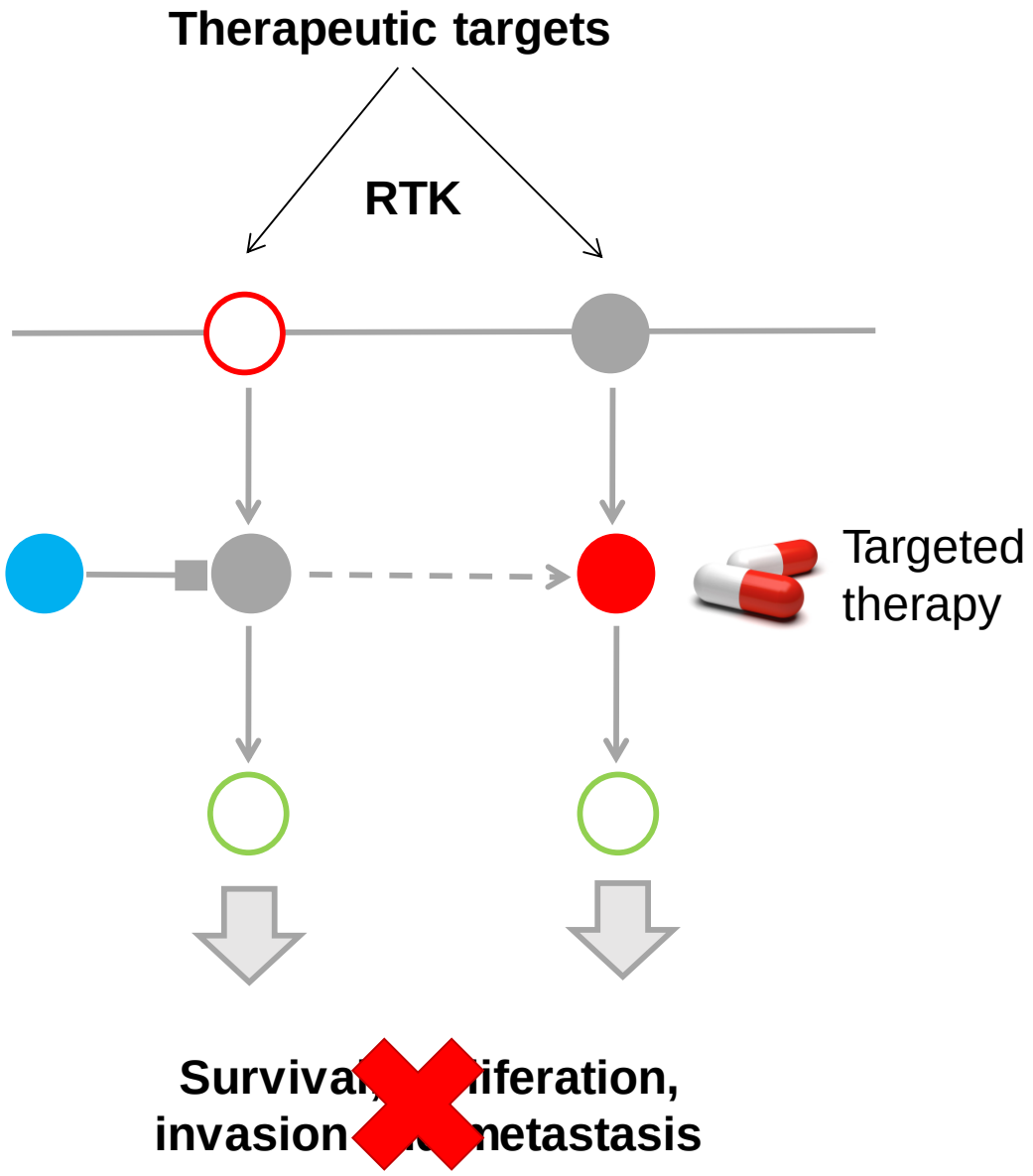
Actionable

Wild-type or No Actionable

Tumor suppressor gene mutated

Oncogene mutated

Druggable



Actionable

Wild-type or No Actionable

Tumor suppressor gene mutated

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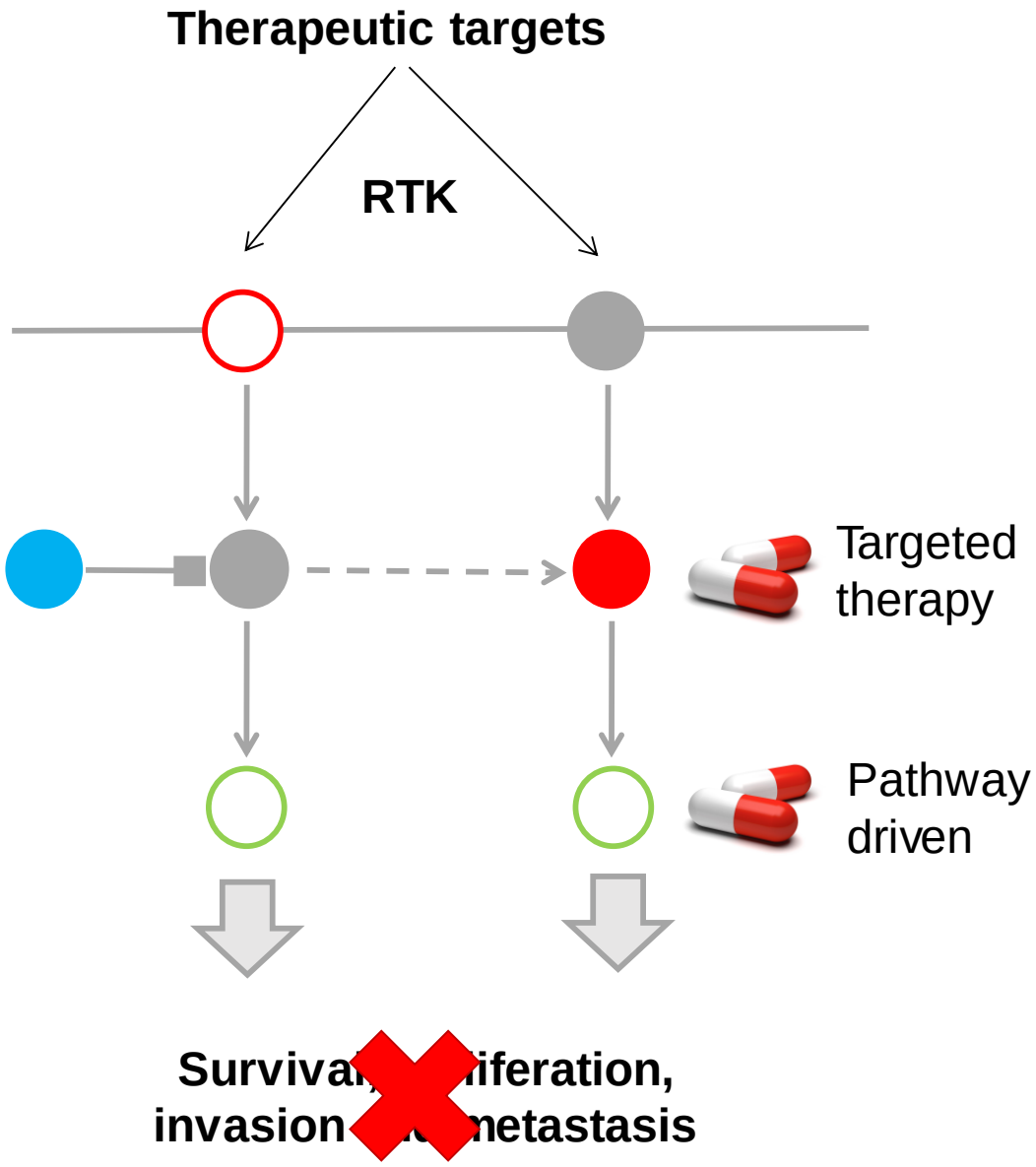
Druggable

1 - Direct pharmacological assignation



Actionable

Wild-type or No Actionable

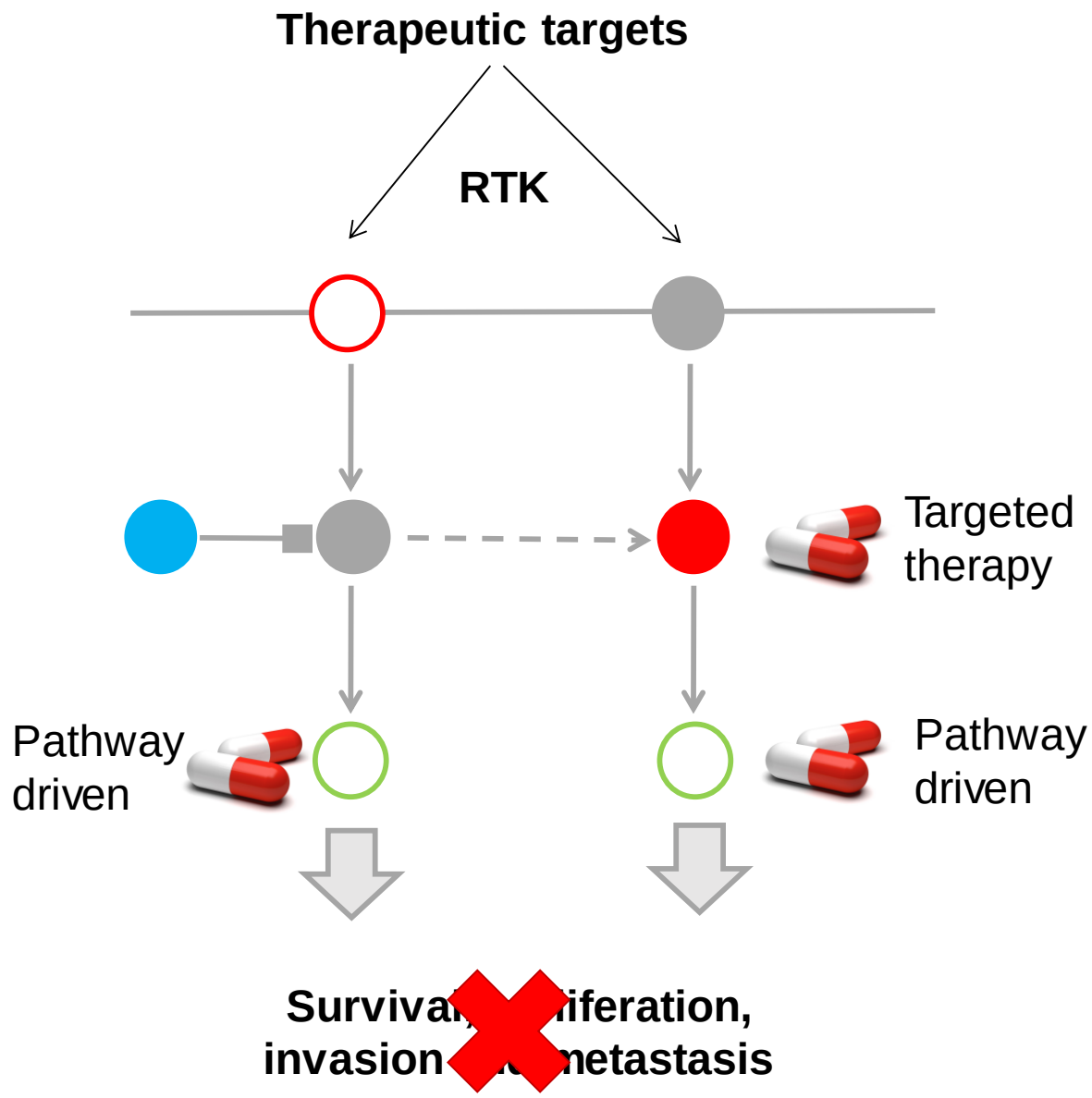
Tumor suppressor gene mutated

Oncogene mutated

Druggable

1 - Direct pharmacological assignation

2 - Indirect pharmacological assignation driven by an oncogene



Actionable

Wild-type or No Actionable

Tumor suppressor gene mutated

Oncogene mutated

Druggable

1 - Direct pharmacological assignation

2 - Indirect pharmacological assignation driven by an oncogene

3 - Indirect pharmacological assignation driven by a tumor suppressor

Drug considerations

- Approval Status

Approval status

Approved

- **Same condition**
- **Other**

→ Repurposing

Clinical trials

- **Same condition clinical trials**
- **Other**

→ Repurposing

Experimental

Withdrawn

Drug considerations

- Approval Status

- Classifications

Target-based classification of drugs

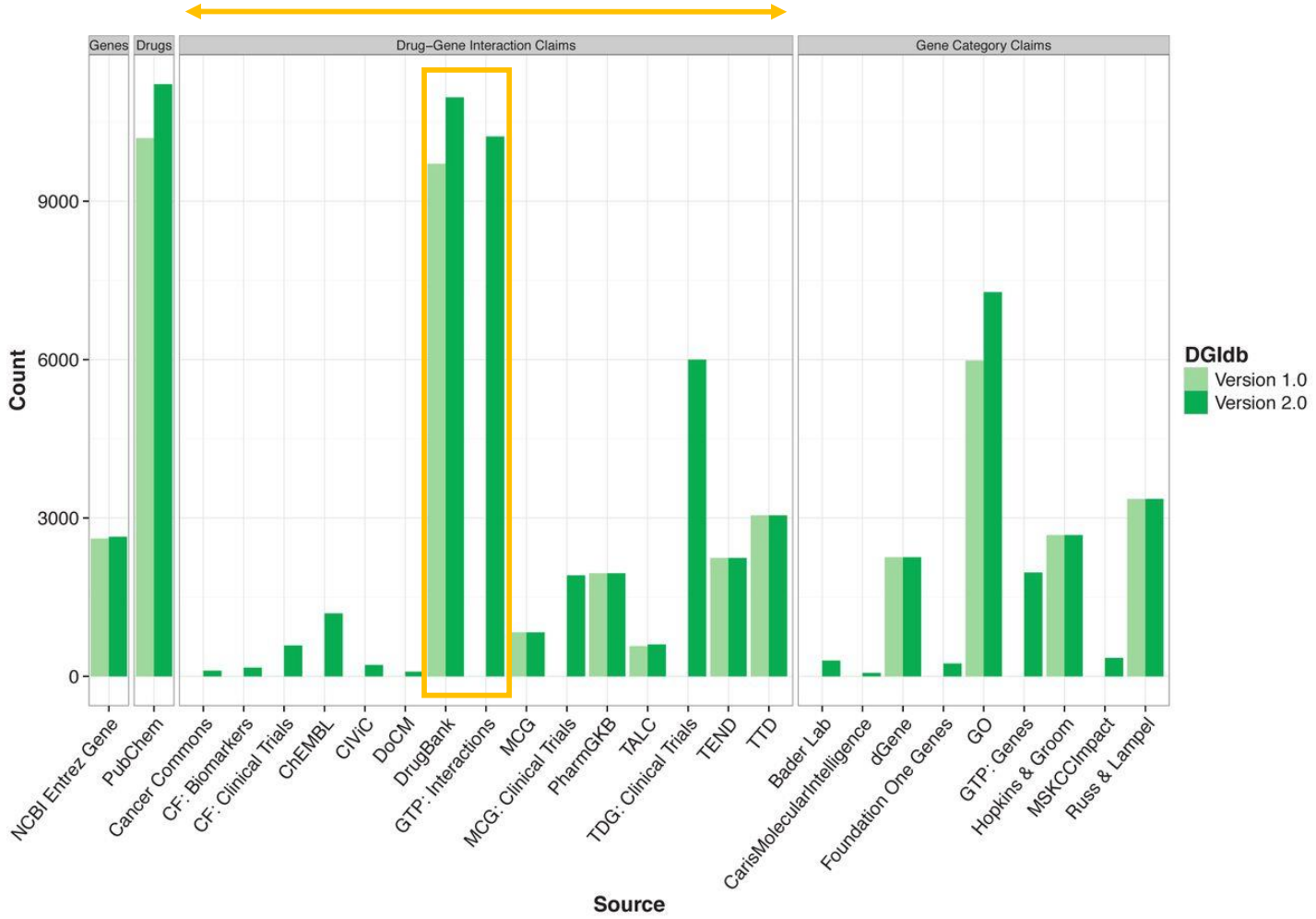
Anatomical Therapeutical Chemical (ATC) classification of drugs

Mechanism of Action (MOA) classification of drugs

Drug considerations

- Approval Status
- Classifications
- Nomenclature
  - Chemical names (IUPAC, SMILES) e.g. 2-acetyloxybenzoic acid (IUPAC)
  - Code Identifiers (CAS) e.g. 50-78-2
  - Generic or nonproprietary names (INN) e.g. acetylsalicylic acid
  - Trade names e.g. Aspirin

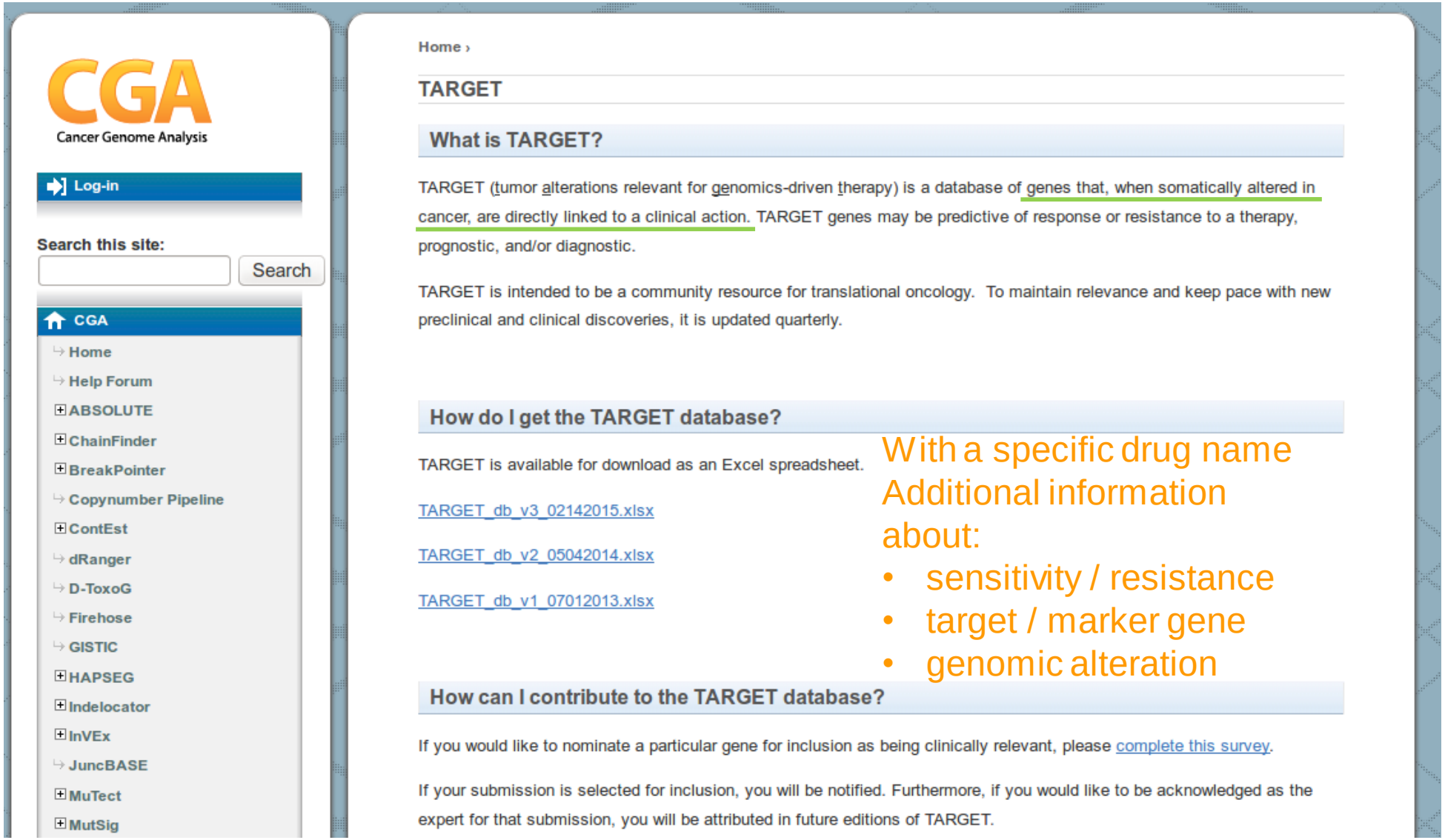
Drug-gene association resources: DGIdb



Cancer Commons: drugs approved or undergoing clinical trials for use in lung, prostate and skin cancer
Clearity Foundation Biomarkers: biomarkers that predict response to selected drugs in ovarian tumors
Clearity Foundation Clinical Trials: clinical trials records based on their relevance to breast and ovarian cancer
DrugBank: large resource detailing drugs and drug-target information
My Cancer Genome: with interactions of specific mutations and therapies
My Cancer Genome Clinical Trials: My Cancer Genome interactions obtained from clinical trials
PharmGKB: with potentially clinically actionable drug-gene associations
TALC: targeted agents in lung cancer
TEND: manual curation of FDA approved drugs and their targets from DrugBank
TTD: therapeutic targets and corresponding drugs

Alex H. Wagner et al. (2016) Nucleic Acids Research

Drug-gene association resources: TARGET



Drug-gene association resources: Monoclonal antibodies

- Highly selective
- Successful treatment in several diseases as rheumatoid arthritis, multiple sclerosis, cancer

  eg. Rituximab in B-cell lymphoma (CD20 (MS4A1))
  Cetuximab in colon cancer (EGFR)

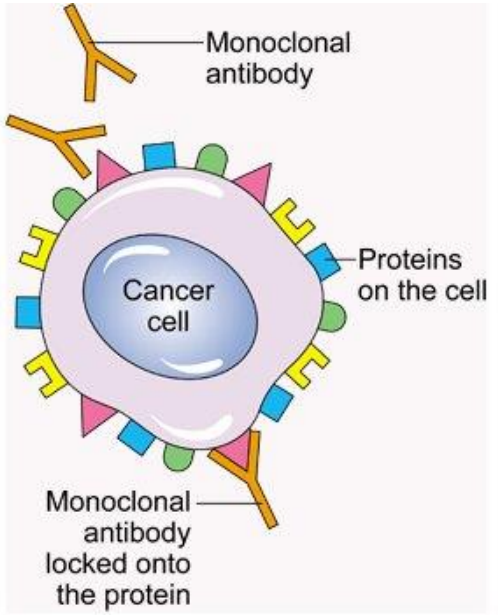


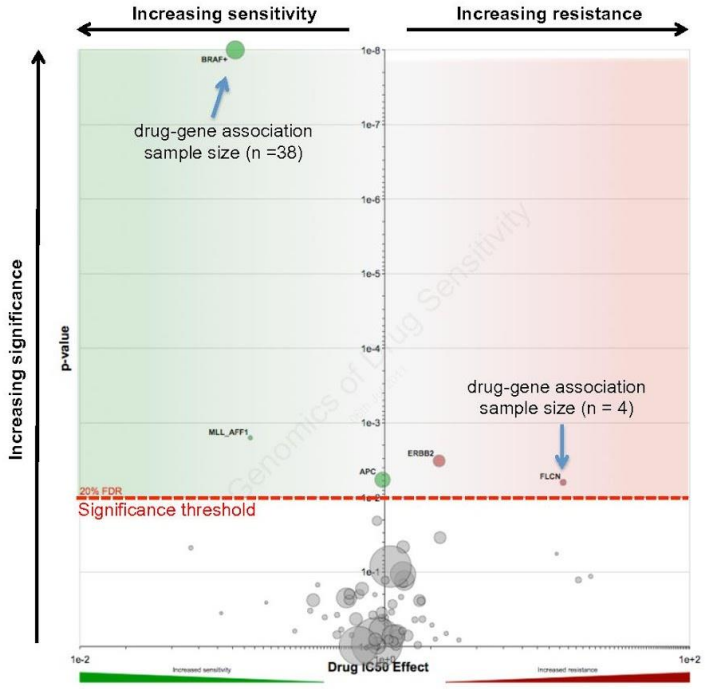
Diagram showing a monoclonal antibody attached to a cancer cell
© CancerHelp UK

https://en.wikipedia.org/wiki/List_of_therapeutic_monoclonal_antibodies

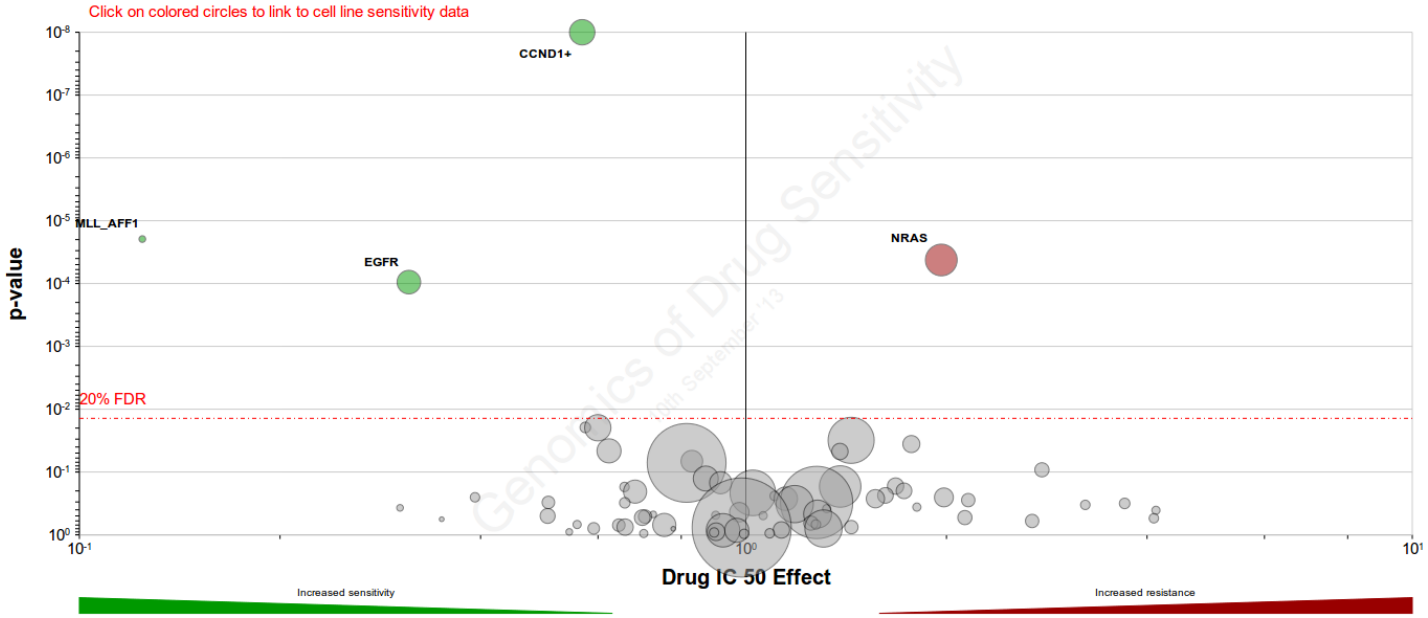
Drug-gene association resources: GDSC

http://www.cancerrxgene.org/

~ 1000 cancer cell lines
mutations, amplifications, deletions, expression data
140 compounds



Gefitinib: EGFR targeted therapy



Gene	Effect	P-value	No. of mutations
CCND1	0.568	6.56e-11	29
MLL_AFF1	0.124	0.0000196	2
NRAS	1.96	0.0000422	45
EGFR	0.312	0.0000950	25
KIT	0.574	0.0195	5
SMAD4	0.600	0.0198	31
KRAS	1.44	0.0313	95
MET	1.77	0.0359	13
FBXW7	0.623	0.0461	26

Drug-gene association resources: CTRP

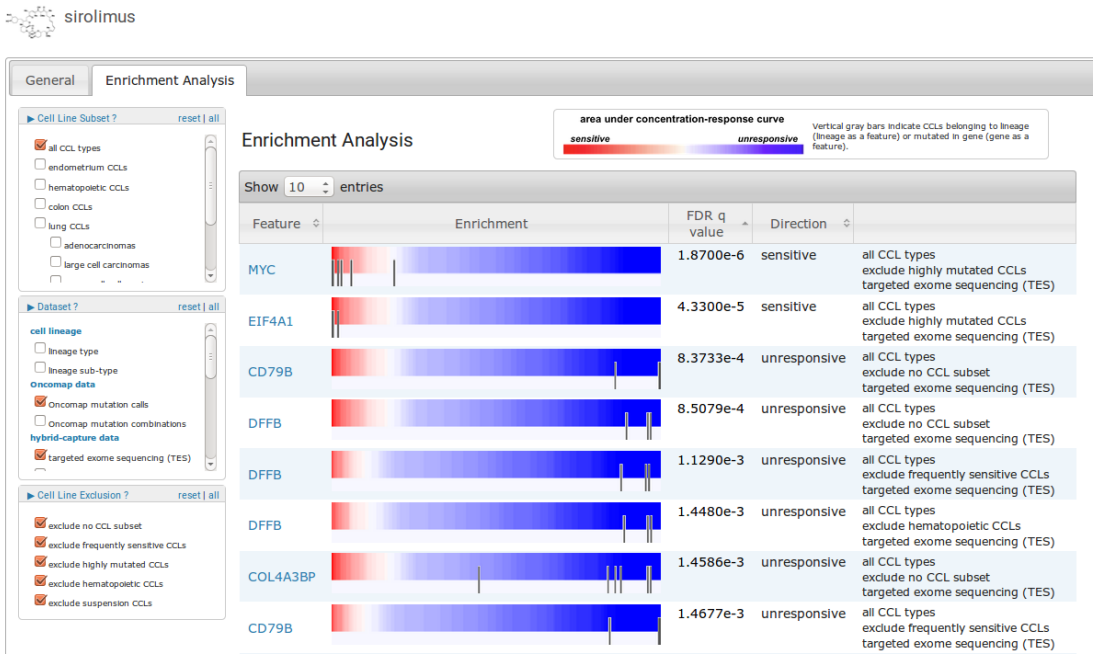
Show 10 entries — Search all columns:

Structure	Name	Synonyms	Targets	Status	starting assay concentration (uM)
	sirolimus	rapamycin;Rapamune	inhibitor of mTOR via FRB domain (in complex with FKBP)	FDA-approved	37

Showing 1 to 1 of 1 entries (filtered from 185 total entries) — First Previous 1 Next Last

http://www.broadinstitute.org/ctrp/

860 cancer cell lines
mutations, CNV, expression data
481small molecules



PANDRUGS

Cancer-oriented computational approach to prioritize and select therapies based on genomic data.

- Definition of a comprehensive catalogue of drugs associated with alterations at gene level.
- A variant/gene prioritization system according to the biological relevance.
- A prioritization system of therapy assignations according to their therapeutic utility in a specific genomic context.

http://pandrugs.bioinfo.cnio.es/#/

PANDRUGS Home Query Login Help API

Welcome to PANDRUGS

A novel method for prioritizing therapies using individual genomic data

Query! ✔

What is PanDrugs?

PanDrugs provides a platform **to guide the selection of therapies from the results of genome-wide studies in cancer disease.**

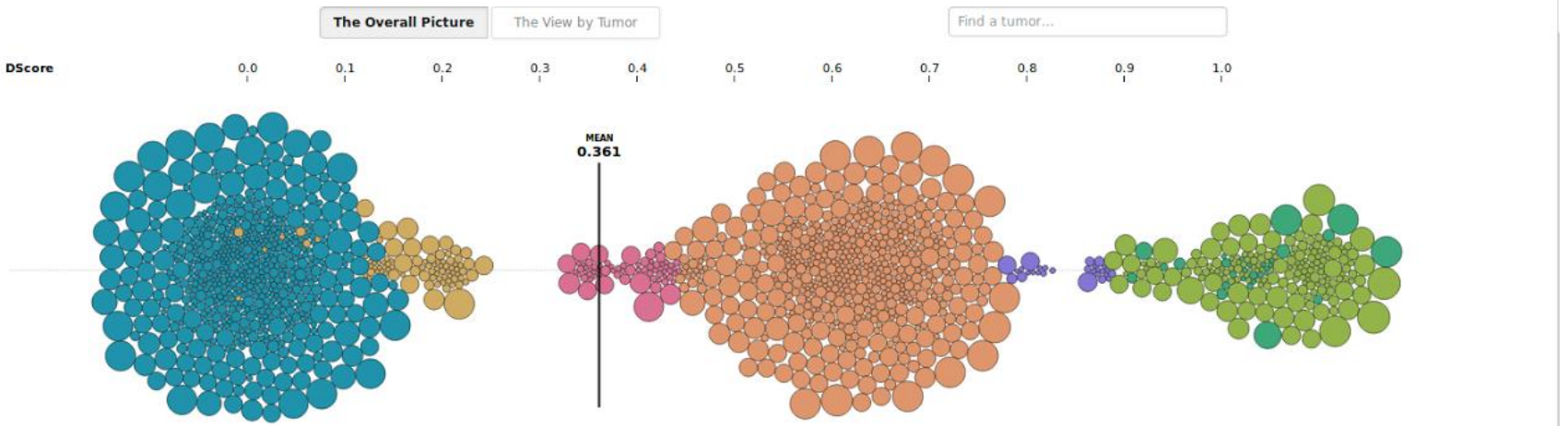
Using 4 alternative inputs (e.g. standard VCF files, RNK files, gene list and drug query), **PanDrugs identify actionable molecular alterations and prioritize drugs by calculating gene-drug scores** which takes into account: i) genomic feature evidence by mutation impact score; ii) target pathway context; iii) drug approval status (FDA, clinical trial or experimental small molecule inhibitors) and iv) manually-curated pharmacological information retrieved from the literature.

PanDrugs scores combines biological and clinical relevance of the genes and their susceptibility to be targeted reflecting the strength or evidence level of the gene-drug association in order to assist the clinical decision making.

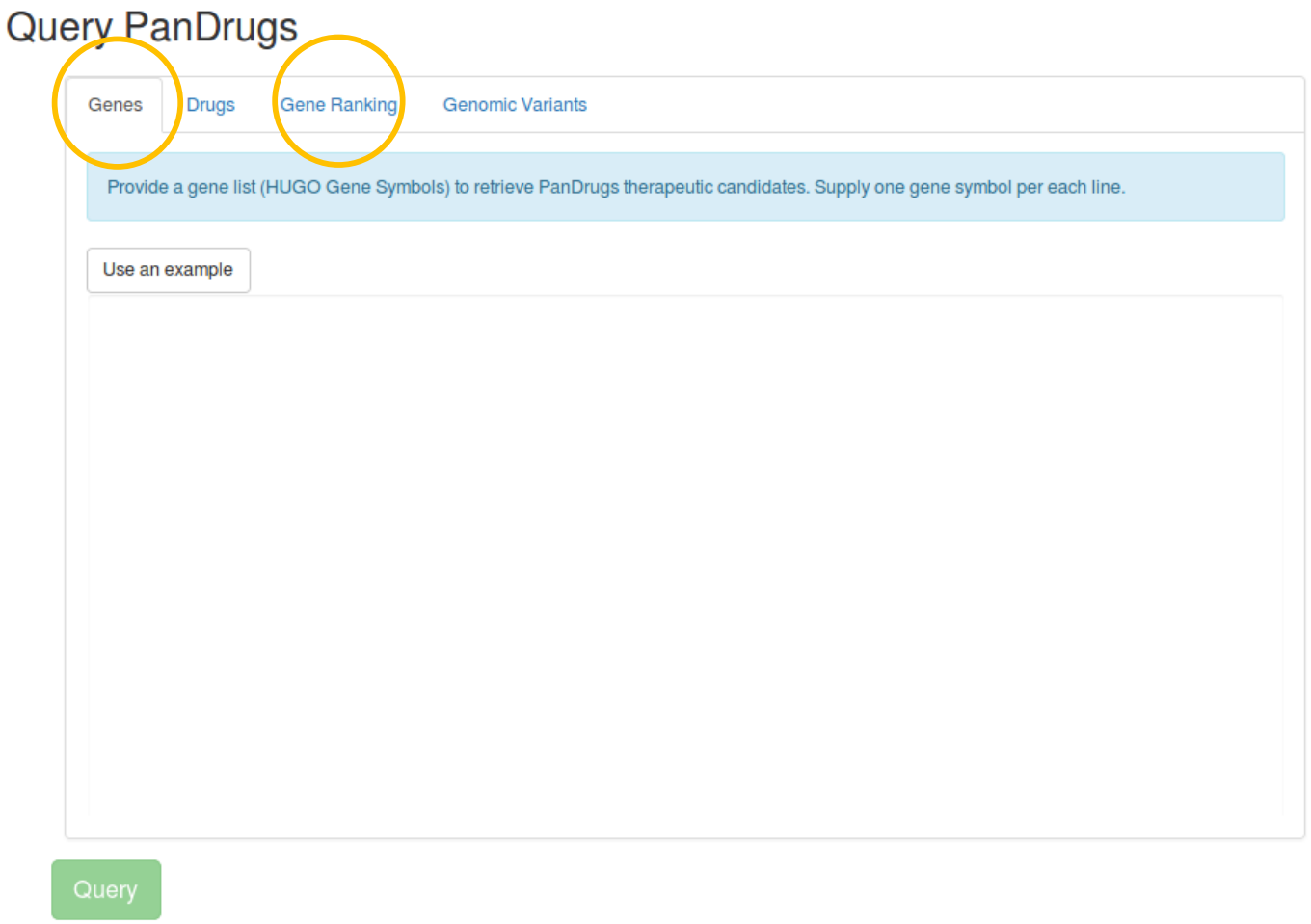
PanDrugs current version integrates data from 18 primary sources and supports ~50,000 drug-target associations obtained from ~6,000 genes and ~11,000 unique compounds.

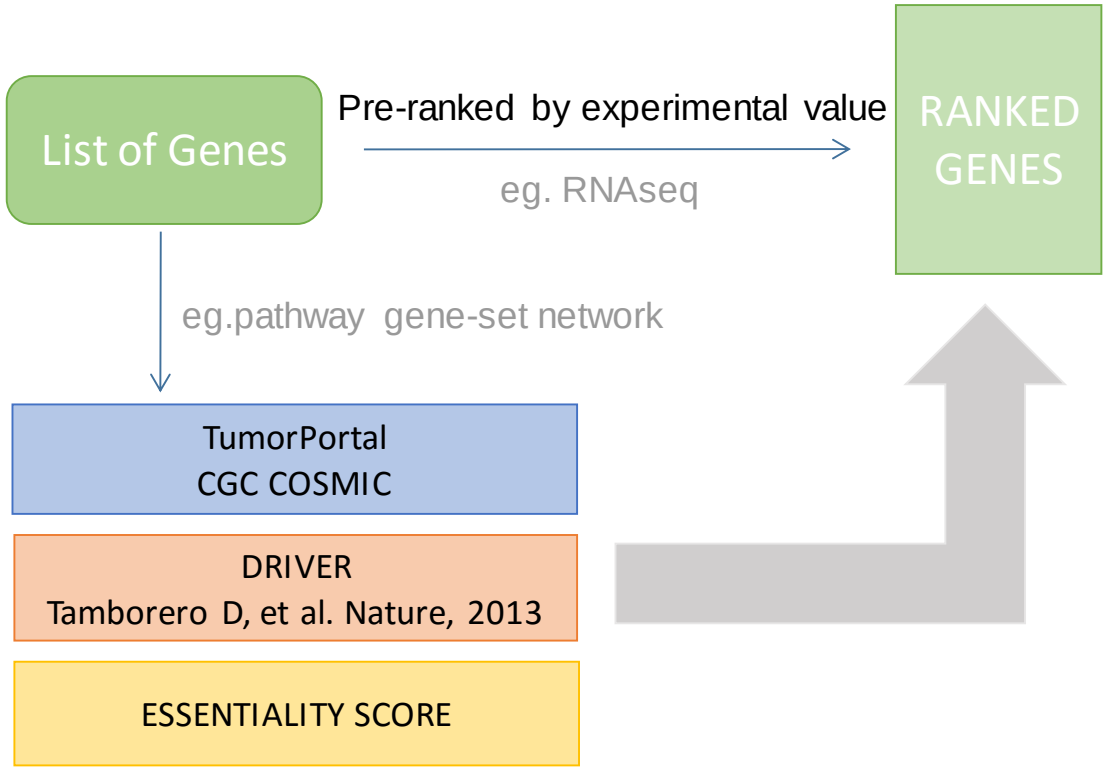
PanDrugs across TCGA tumoral landscape (by Drugs Genes)

This plot shows the percentage of patients in different tumor types from TCGA study that would be treated according to PanDrugs suggestions based on punctual genetic alterations. Each bubble represents a treatment with a particular drug and the drug score is the highest one among the computed for each patient that could be treated with that compound. Only alterations with a gene score greater or equal than 0.6 are considered.



Input options

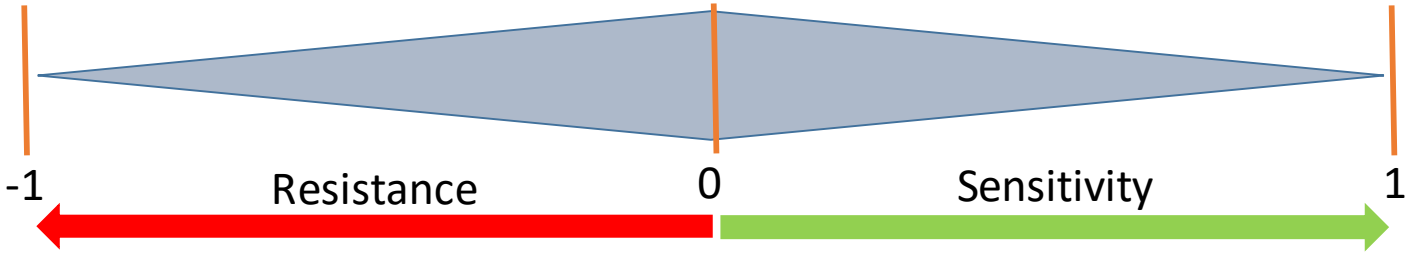


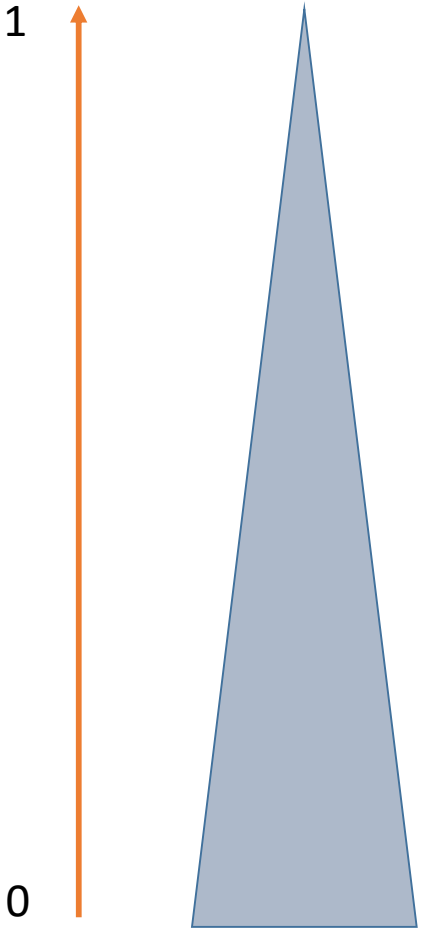


Gene prioritization system

Gene Score (GScore) calculation

Drug Relevance (DScore)





CANCER	DRUG STATUS	GENE	SCORE
Cancer	Approved	target	± 1
		marker	± 0.9
Clinical trials cancer		target	± 0.8
		marker	± 0.7
Cancer	Clinical trials	target	± 0.6
		marker	± 0.5
Other conditions	Approved	target	± 0.4
		marker	± 0.3
	Clinical trials	target	± 0.2
		marker	± 0.1
	Experimental	target	± 0.0008
		marker	± 0.0004

Pre-calculated values

Drug Relevance (DScore)

Approved and Clinical trials:

Gene factor = # genes (max. 9) - 1 (if indirect and no marker evidence)
Source factor = # expert curated sources (max 9)

DScore = Pre-computed value - 0.1 + (0.01 * Gene Factor) + 0.001 + (0.001 * Source Factor)

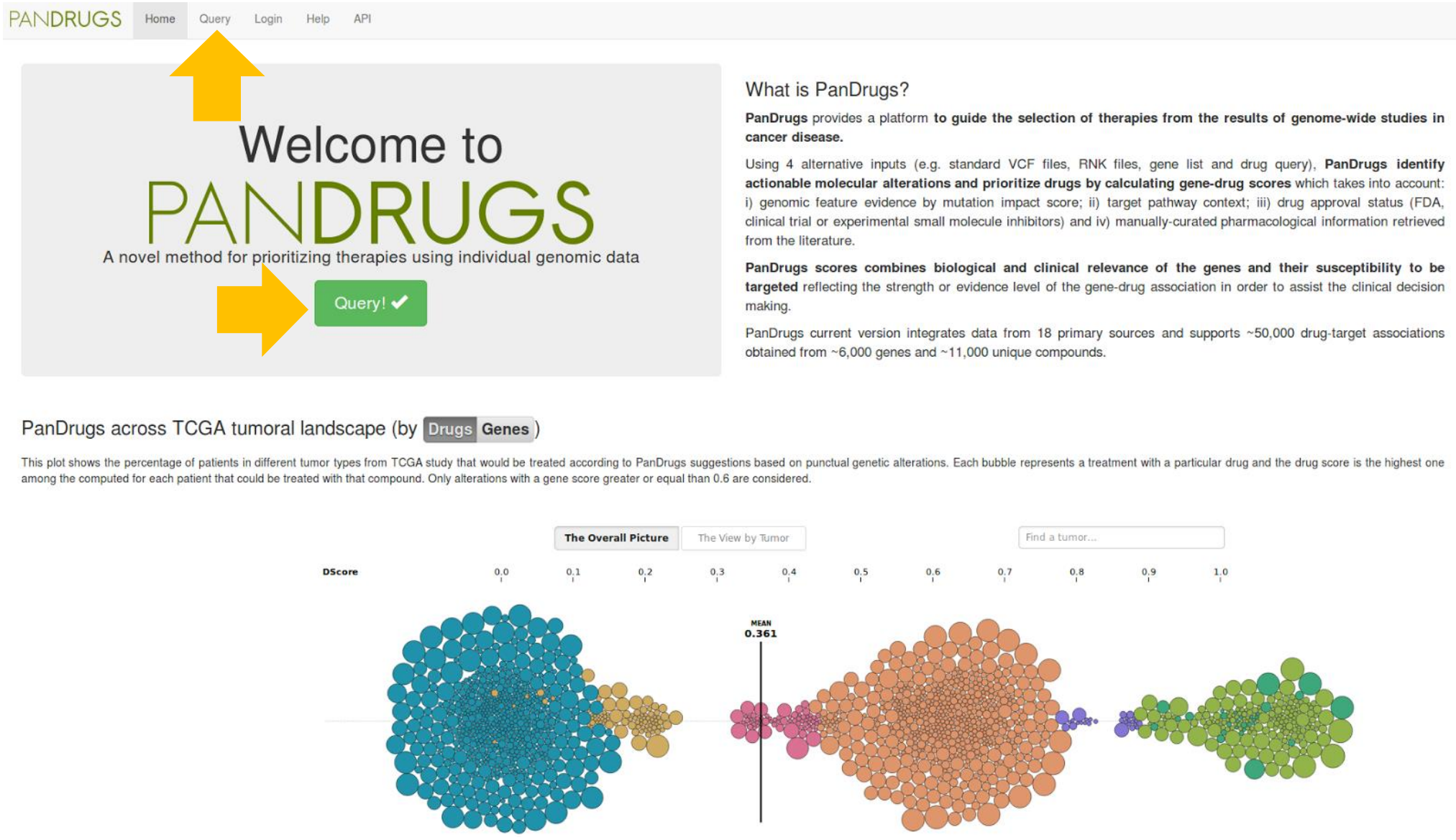
Experimental:

DScore = Pre-computed value - 0.0002 (if indirect)

INDIRECT assignations will have a lower DScore unless a marker evidence supports the association.

If one drug has a sensitivity response due to one gene, but a resistance response due to another one, the drug assignation is updated as RESISTANCE and the score turn into negative.

Gene search example



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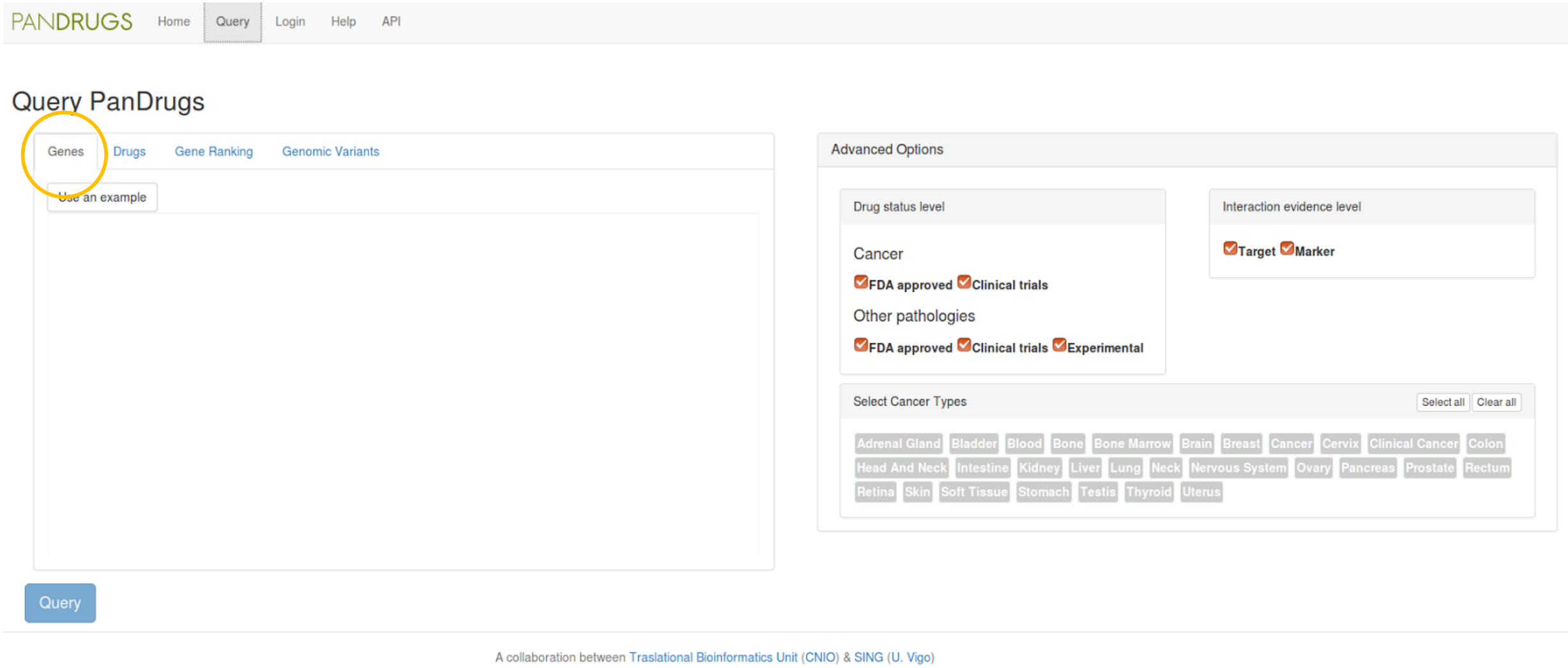
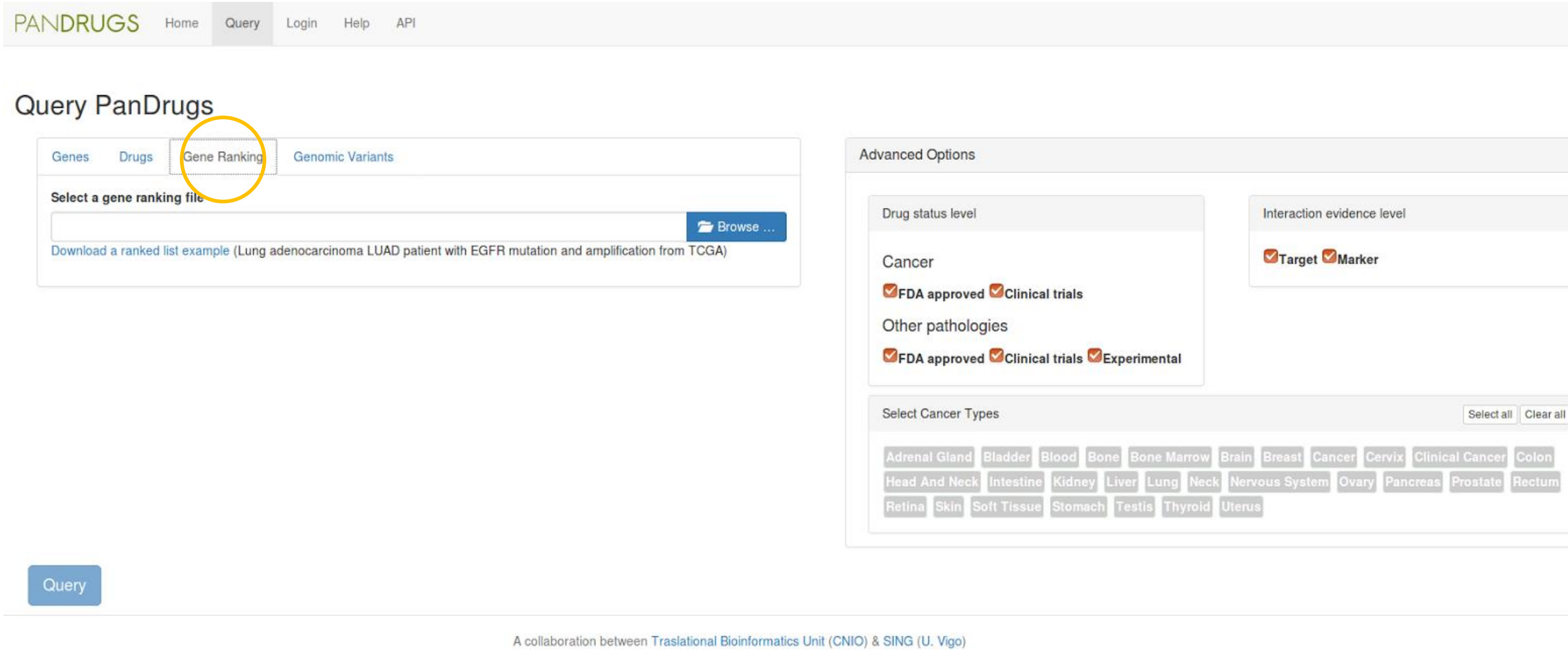
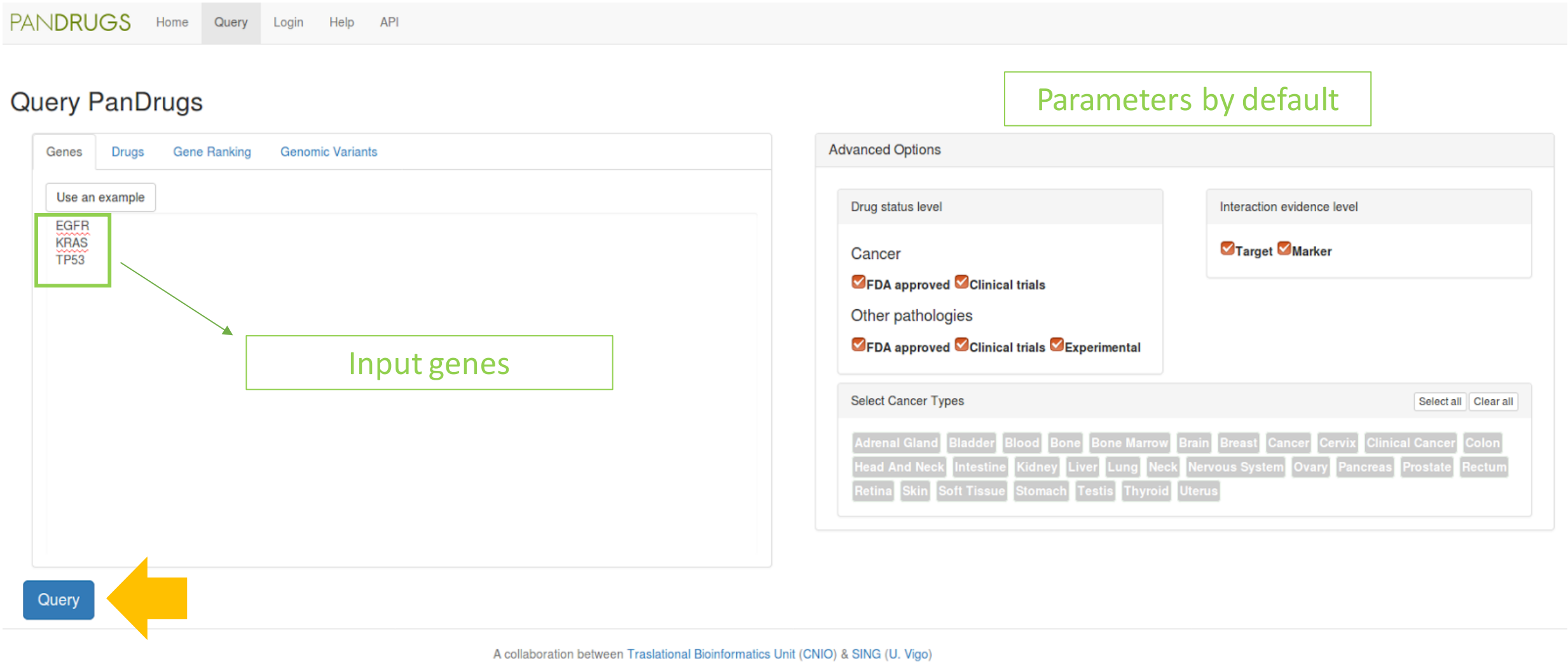


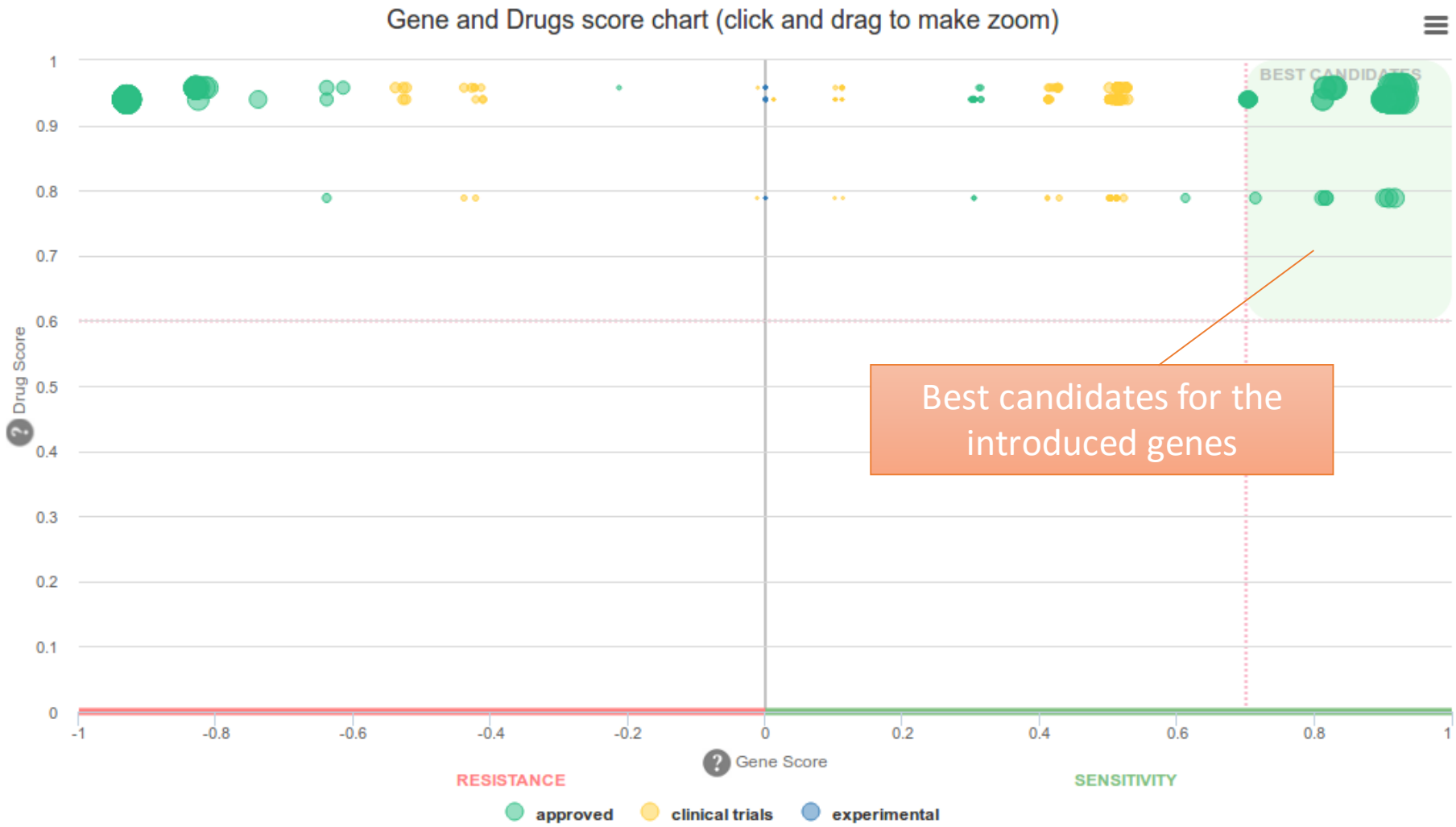
Gene search example



Gene search example



Gene search example



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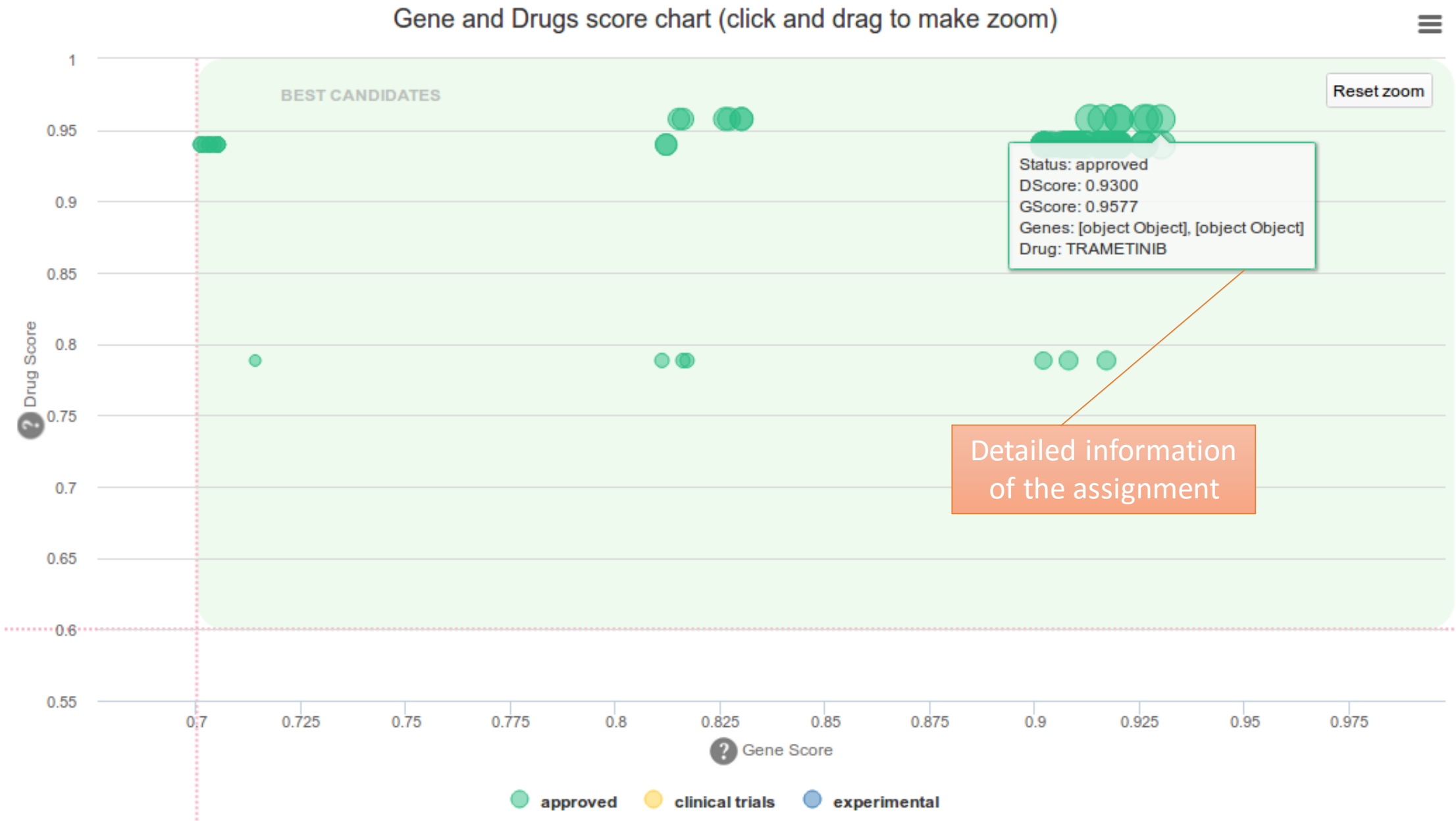
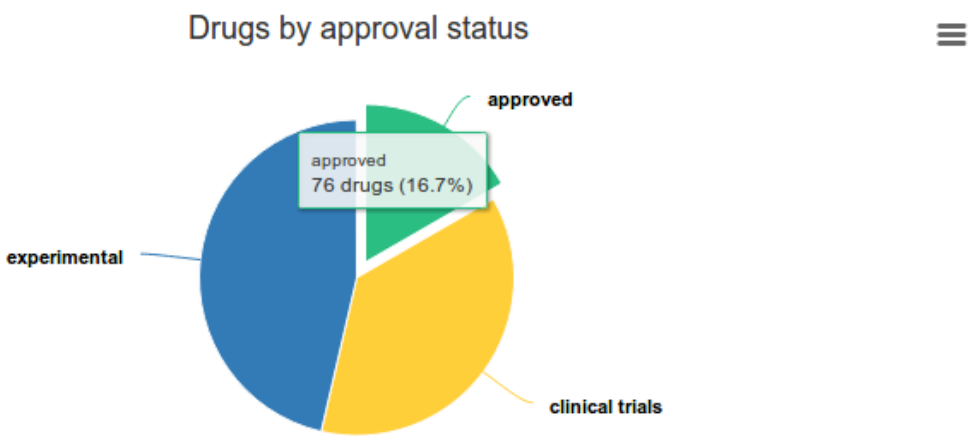
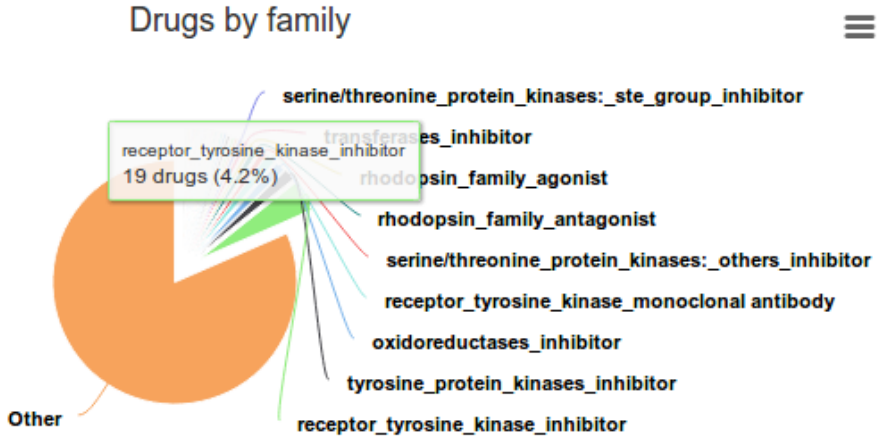


Gene search example





Gene search example

Download as CSV

Actions	Gene(s)	Drug	Family	Source(s)	Drug status	Type of therapy	Interaction	▼DScore	GScore
+	EGFR and KRAS	TRAMETINIB	serine/threonine_protein_kinases:_ste_group_inhibitor	CIV CC CFB DoCM DB GtPI MCG MCGCT TALC TCT	Approved for skin cancer	Targeted therapy	G→T⊣D	0.9300	0.9577
+	EGFR and KRAS	CETUXIMAB	receptor_tyrosine_kinase_monoclonal antibody	CIV CC CFB DoCM DB GtPI MCG PGKB TALC TCGA TEND TTD TCT moAb	Approved for colon and rectum cancer	Targeted therapy	T⊣D	0.9300	0.9577
+	EGFR and KRAS	COBIMETINIB	Other	CC CFB DB MCG MCGCT TALC TCT	Approved for skin cancer	Targeted therapy	G→T⊣D	0.9270	0.9577
+	EGFR and KRAS	REGORAFENIB	receptor_tyrosine_kinase_inhibitor	DB GtPI MCG MCGCT TALC TCT	Approved for colon, intestine, rectum and stomach cancer	Targeted therapy	G→T⊣D	0.9260	0.9577
+	EGFR	TRASTUZUMAB	receptor_tyrosine_kinase_monoclonal antibody	CIV CFB CFCT DoCM DB GtPI MCG PGKB TALC TCGA TEND TTD TCT moAb	Approved for breast and stomach cancer	Targeted therapy	T⊣D	0.9200	0.9398
+	EGFR	LAPATINIB	receptor_tyrosine_kinase_inhibitor	CIV CC CFB CFCT DoCM DB GDSC GtPI MCG PGKB TALC TCGA TEND TTD TCT	Approved for breast cancer	Targeted therapy	T⊣D	0.9200	0.9398
+	EGFR and KRAS	SORAFENIB	receptor_tyrosine_kinase_inhibitor	CIV CFCT DoCM DB GDSC GtPI MCG MCGCT PGKB TALC TCGA TEND TTD TCT	Approved for kidney cancer	Targeted therapy	G→T⊣D	0.9200	0.9577
+	EGFR	PERTUZUMAB	receptor_tyrosine_kinase_monoclonal antibody	CFB DoCM DB GtPI MCG PGKB TALC TCGA TTD TCT moAb	Approved for breast cancer	Targeted therapy	T⊣D	0.9190	0.9398
+	TP53	PACLITAXEL	rhodopsin_family_antagonist	CIV CFB CFCT DB GDSC GtPI PGKB TEND TTD TCT	Approved for breast, lung, ovary and pancreas cancer	Chemotherapy	G→T⊣D	0.9170	0.7884
+	EGFR	AFATINIB	receptor_tyrosine_kinase_inhibitor	CC DB GDSC GtPI MCG MCGCT TALC TTD TCT	Approved for lung cancer	Targeted therapy	T⊣D	0.9170	0.9398

Gene search example

Actions	Gene(s)	Drug	Family	Source(s)	Drug status	Type of therapy	Interaction	▼DScore	GScore
−	EGFR and KRAS	TRAMETINIB	serine/threonine_protein_kinases:_ste_group_inhibitor	CIV CC CFB DoCM DB GtPI MCG MCGCT TALC TCT	Approved for skin cancer	Targeted therapy	G→T⊣D	0.9300	0.9577
	TRAMETINIB is a drug approved by FDA that acts as an inhibitor of MAP2K1, a protein downstream to EGFR and KRAS **EGFR and KRAS** Sensitivity: SENSITIVITY / RESISTANCE Alteration: WT (sensitivity) / Missense_mutation (resistance) Find more info for "TRAMETINIB"+"MAP2K1" in: [PubMed] [ClinicalTrials.gov]		serine/threonine_protein_kinases:_ste_group_inhibitor	CIViC, CancerCommons, ClearityFoundationBiomarkers, DoCM, DrugBank, GuideToPharmacologyInteractions, MyCancerGenome, MyCancerGenomeClinicalTrial, TALC, TdgClinicalTrial			G→T⊣D See pathways	0.9300	0.9577
	Molecular alterations in KRAS are associated with response to TRAMETINIB, a drug approved by FDA **KRAS** Sensitivity: SENSITIVITY Alteration: Missense_mutation Find more info for "TRAMETINIB"+"KRAS" in: [PubMed] [ClinicalTrials.gov]		serine/threonine_protein_kinases:_ste_group_inhibitor	CIViC, CancerCommons, ClearityFoundationBiomarkers, DoCM, DrugBank, GuideToPharmacologyInteractions, MyCancerGenome, MyCancerGenomeClinicalTrial, TALC, TdgClinicalTrial			T⋯⋯D	0.8300	0.9577