Precision medicine: NGS variant analysis and interpretation for translational research

PanDrugs: Matching mutations with therapies

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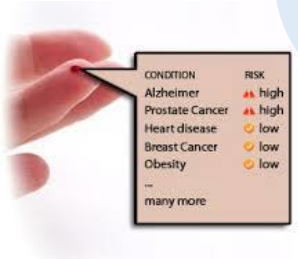
September 29, 2016

Centro Nacional de Investigaciones Oncológicas

INSTITUTO GULBENKIAN DE CIÊNCIA

Predisposition



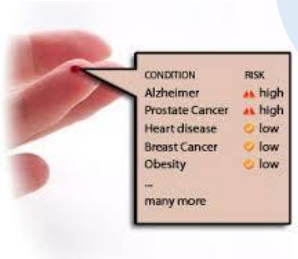
Prognosis

Genomic alterations

Diagnosis

Treatment

Predisposition



Prognosis

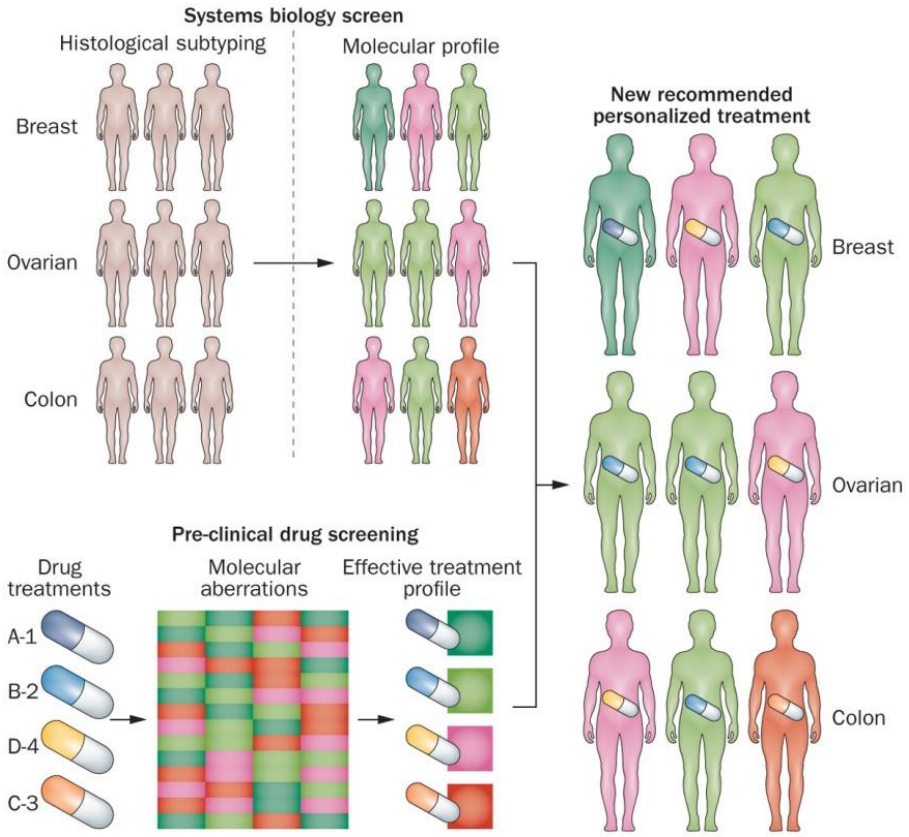
Genomic alterations

Diagnosis

Treatment

Pharmacogenomic association

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

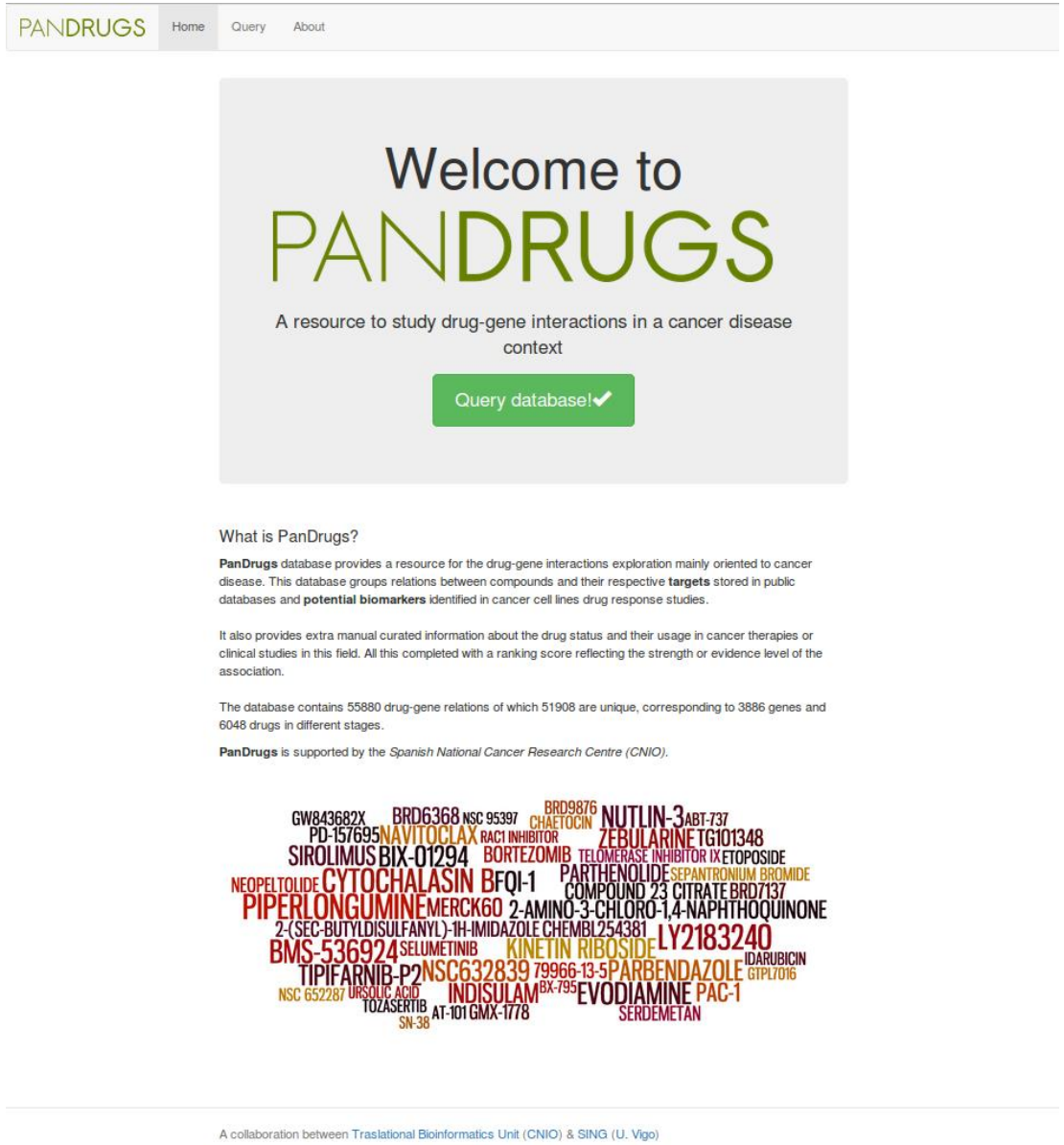
Werner, H. M. J. et al. (2014) Cancer Systems Biology: a peek into the future of patient care?Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2014.6

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.

Web page



Daniel Glez-Peña

Miguel Reboiro-Jato

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

38628 unique drug-gene relations
4236 genes
10831 drugs

cnio Centro Nacional de Investigaciones Oncológicas

SING Next Generation Computer Systems Group
Upgrading your knowledge
Sistemas Informáticos de Nueva Generación

Sources

DGIdb
THE DRUG GENE INTERACTION DATABASE

Cancer Commons
CIViC
The Clearity Foundation
DoCM
DrugBank
Guide to PHARMACOLOGY
My Cancer Genome
PharmGKB
TTD
TALC
TDG
TEND

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

Therapeutic monoclonal antibodies

MoAb - Drug-gene interactions

CGA
Cancer Genome Analysis

TARGET
(Tumor Alterations Relevant for Genomics driven Therapy)

Drug-gene interactions

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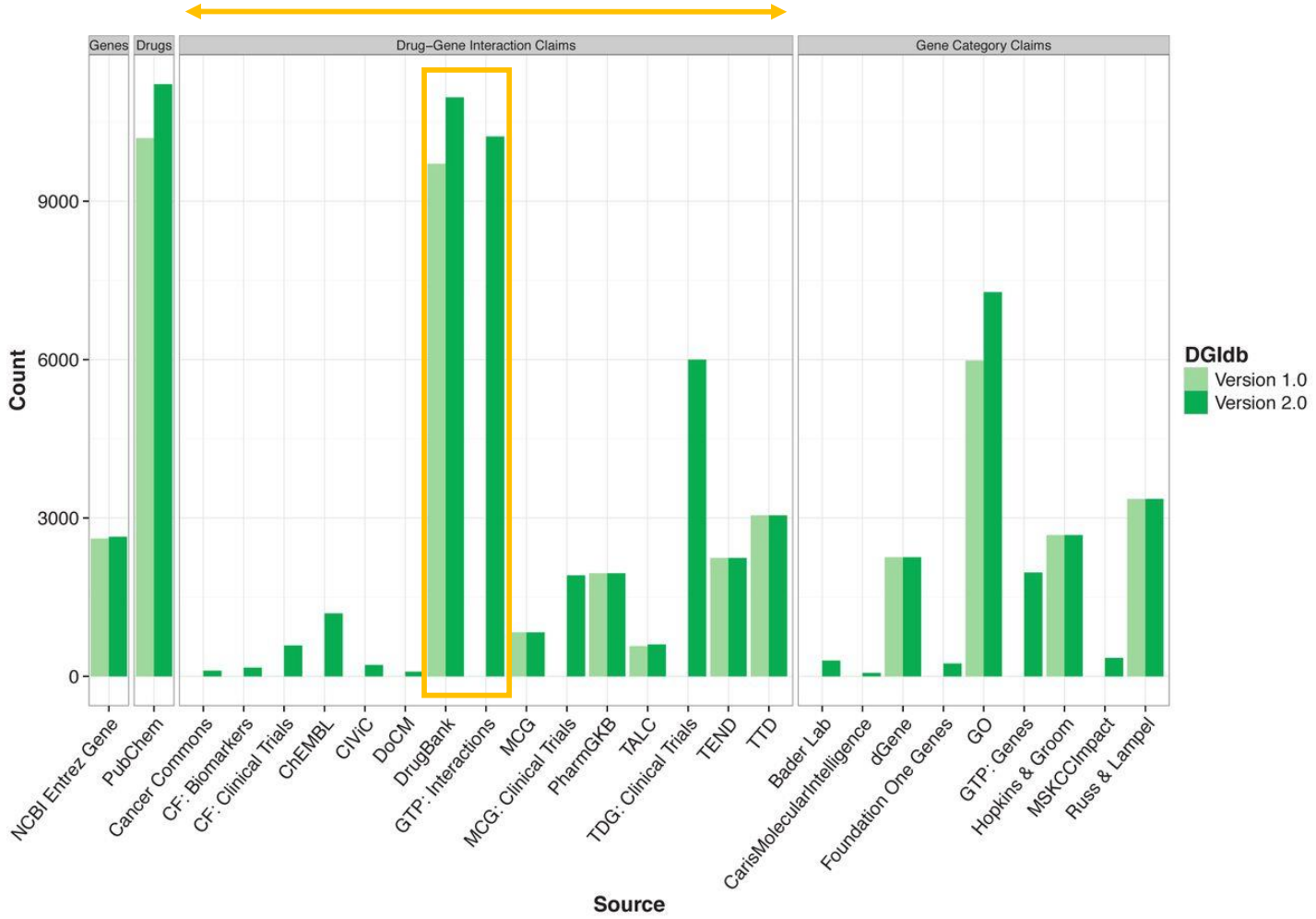
Rees et al. (2016)Nat Chem Biol

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

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)

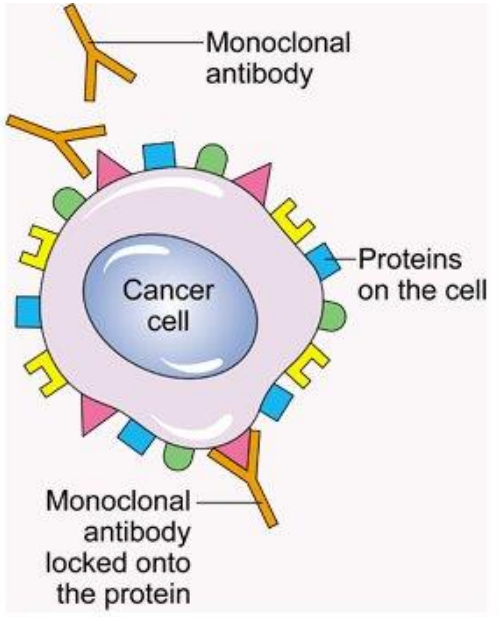


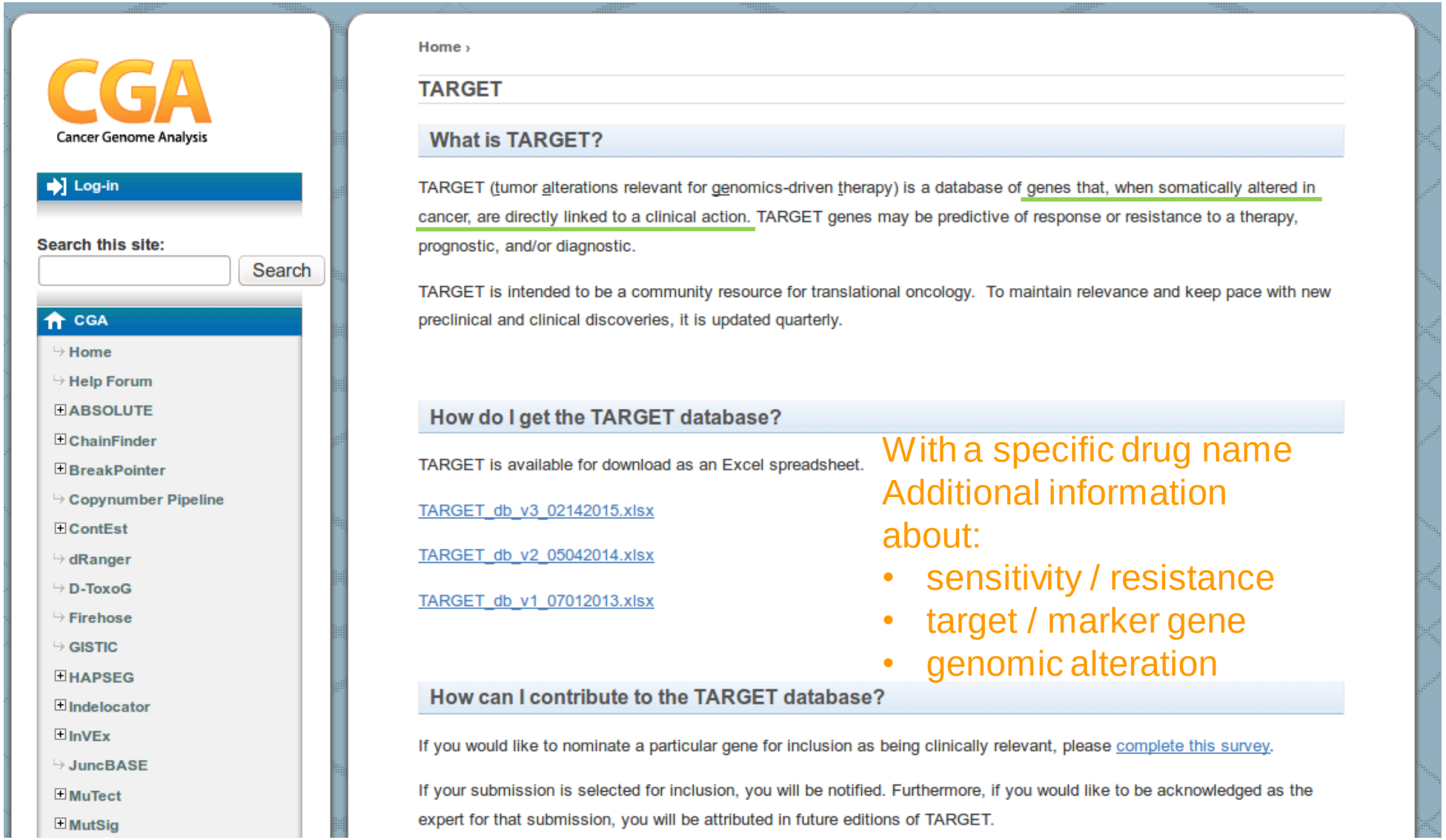
Diagram showing a monoclonal antibody attached to a cancer cell
© CancerHelp UK

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

- Employed in therapy and prevention
- Interacting with human proteins
- With an existing gene symbol

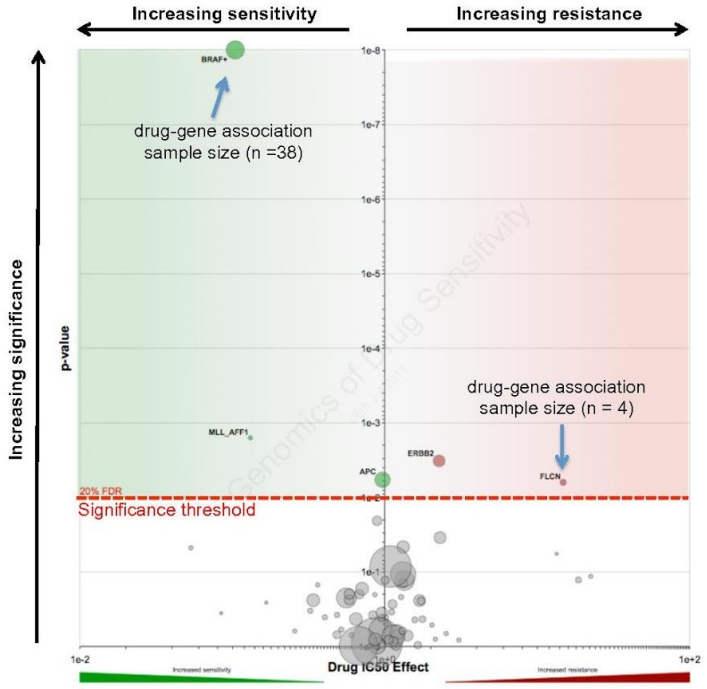
Additional monoclonal antibodies relations found in literature

TARGET


CGA
Cancer Genome Analysis
Log-in
Search this site:
Search
CGA
Home
Help Forum
ABSOLUTE
ChainFinder
BreakPointer
Copynumber Pipeline
ContEst
dRanger
D-ToxoG
Firehose
GISTIC
HAPSEG
Indelocator
InVEx
JuncBASE
MuTect
MutSig
Home ›
TARGET
What is TARGET?
TARGET (tumor alterations relevant for genomics-driven therapy) is a database of genes that, when somatically altered in cancer, are directly linked to a clinical action. TARGET genes may be predictive of response or resistance to a therapy, prognostic, and/or diagnostic.
TARGET is intended to be a community resource for translational oncology. To maintain relevance and keep pace with new preclinical and clinical discoveries, it is updated quarterly.
How do I get the TARGET database?
TARGET is available for download as an Excel spreadsheet.
TARGET_db_v3_02142015.xlsx
TARGET_db_v2_05042014.xlsx
TARGET_db_v1_07012013.xlsx
With a specific drug name
Additional information about:
• sensitivity / resistance
• target / marker gene
• genomic alteration
How can I contribute to the TARGET database?
If you would like to nominate a particular gene for inclusion as being clinically relevant, please complete this survey.
If your submission is selected for inclusion, you will be notified. Furthermore, if you would like to be acknowledged as the expert for that submission, you will be attributed in future editions of TARGET.

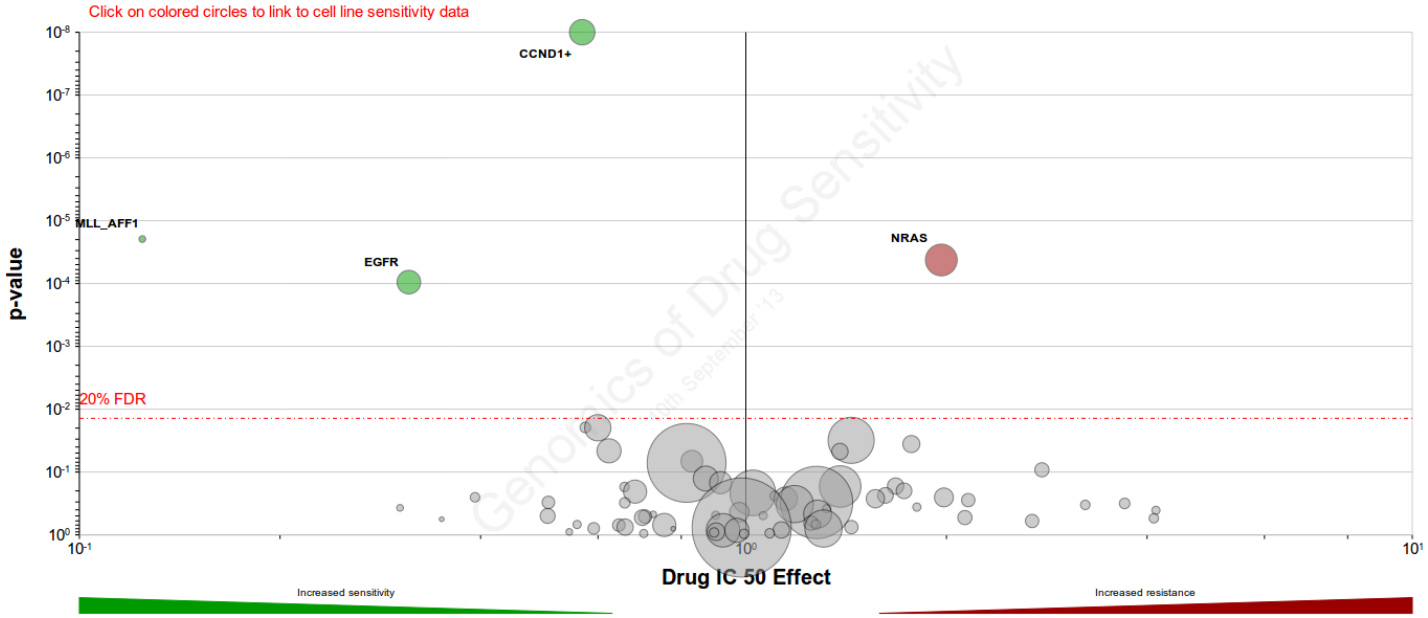
GDSC

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



http://www.cancerrxgene.org/

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

CTRP

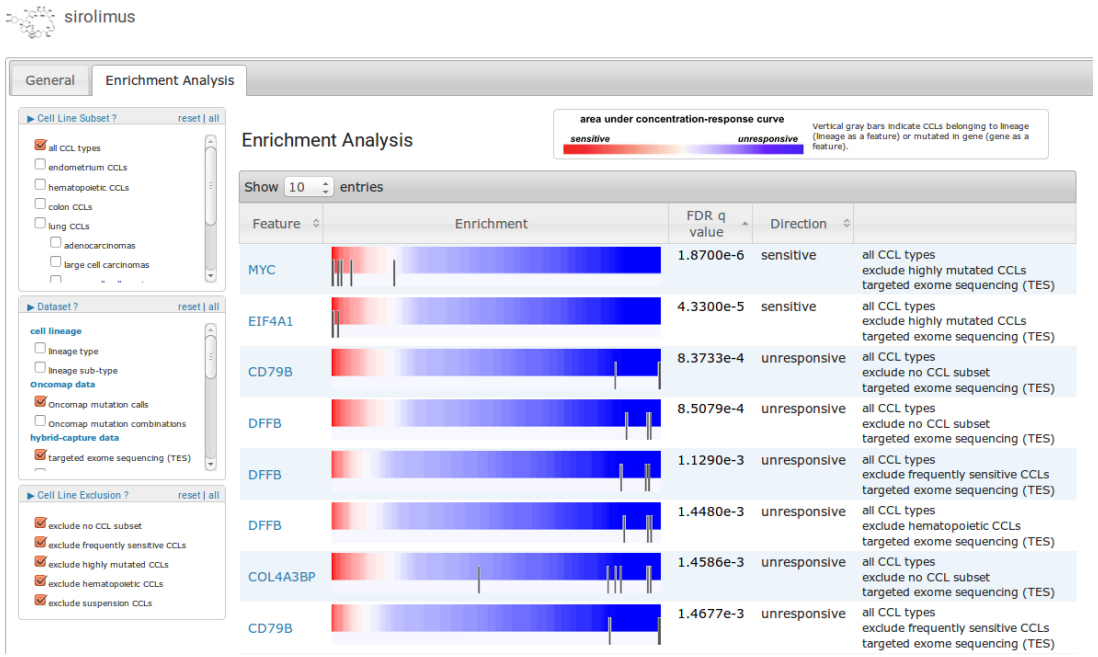
Show 10 entries — Search all columns:

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)

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

242 cancer cell lines
mutations, CNV, expression data
354 small molecules



Sources

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ChemSpider
Search and share chemistry

Standardization of the drug name

Approval status

Approved
- **Tumor type** ⇢
- **Cancer clinical trials** ⇢ Repurposing
- **Other** →

Clinical trials
- **Cancer clinical trials** ⇢ Repurposing
- **Other** →

Experimental

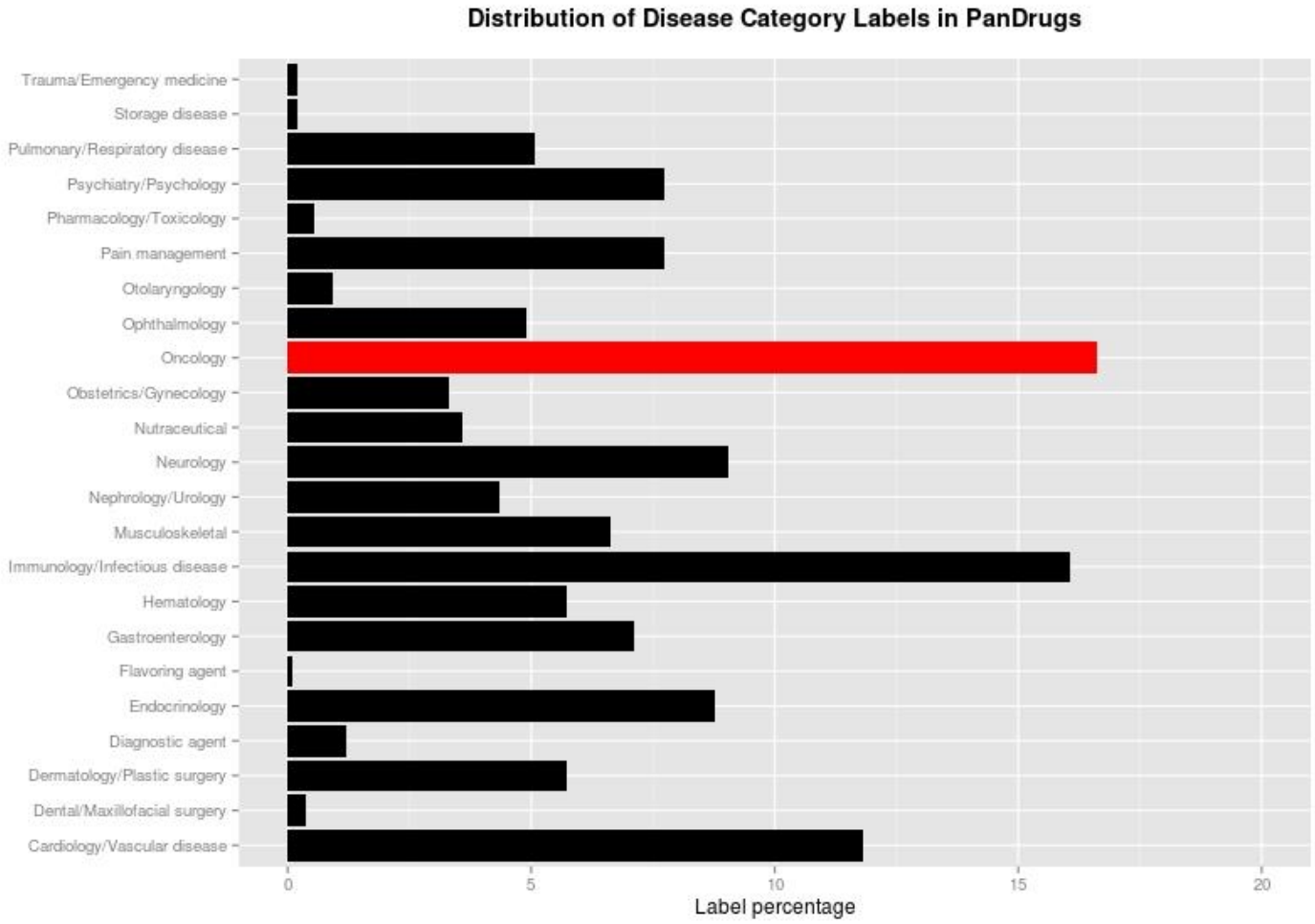
Withdrawn

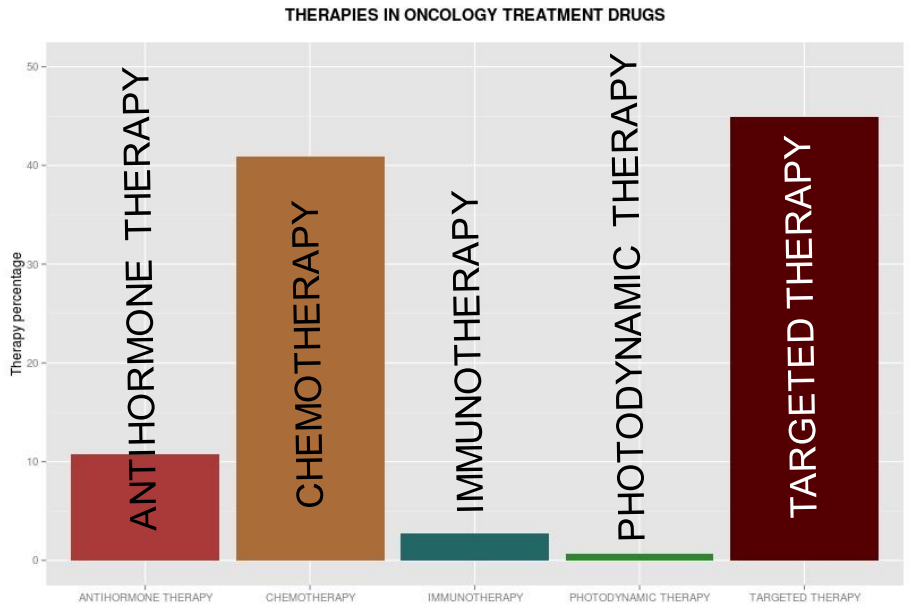
Undefined

FDA U.S. FOOD & DRUG ADMINISTRATION

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

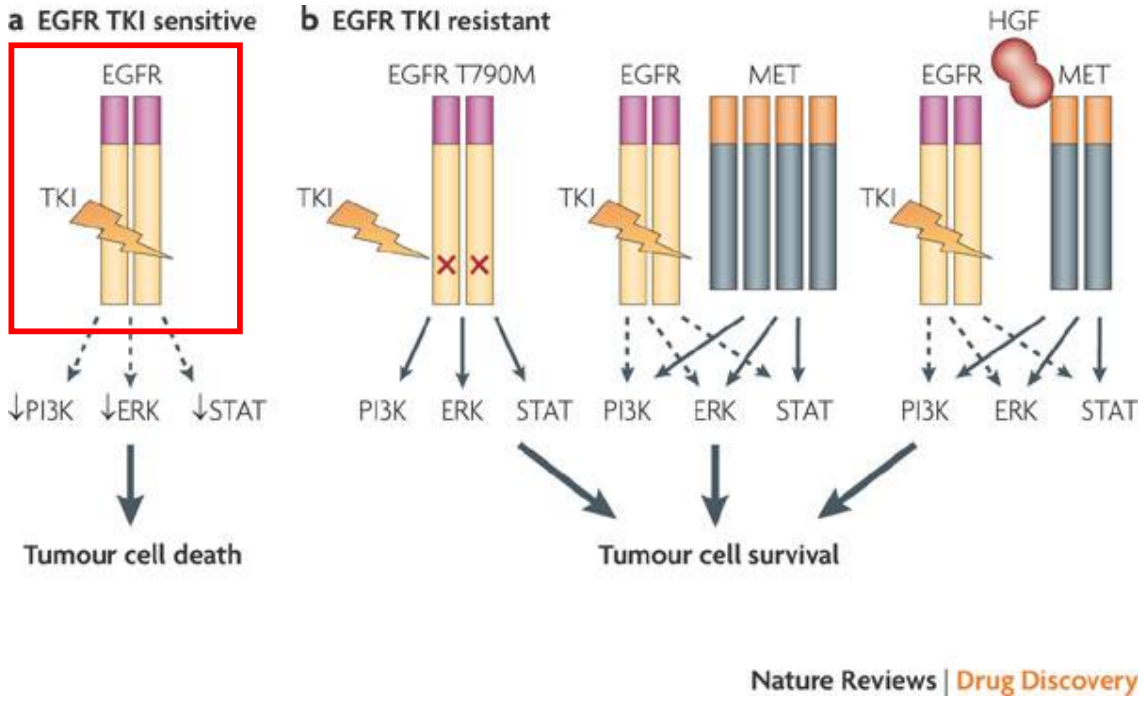
Pathological area and cancer therapy type





Target & marker genes

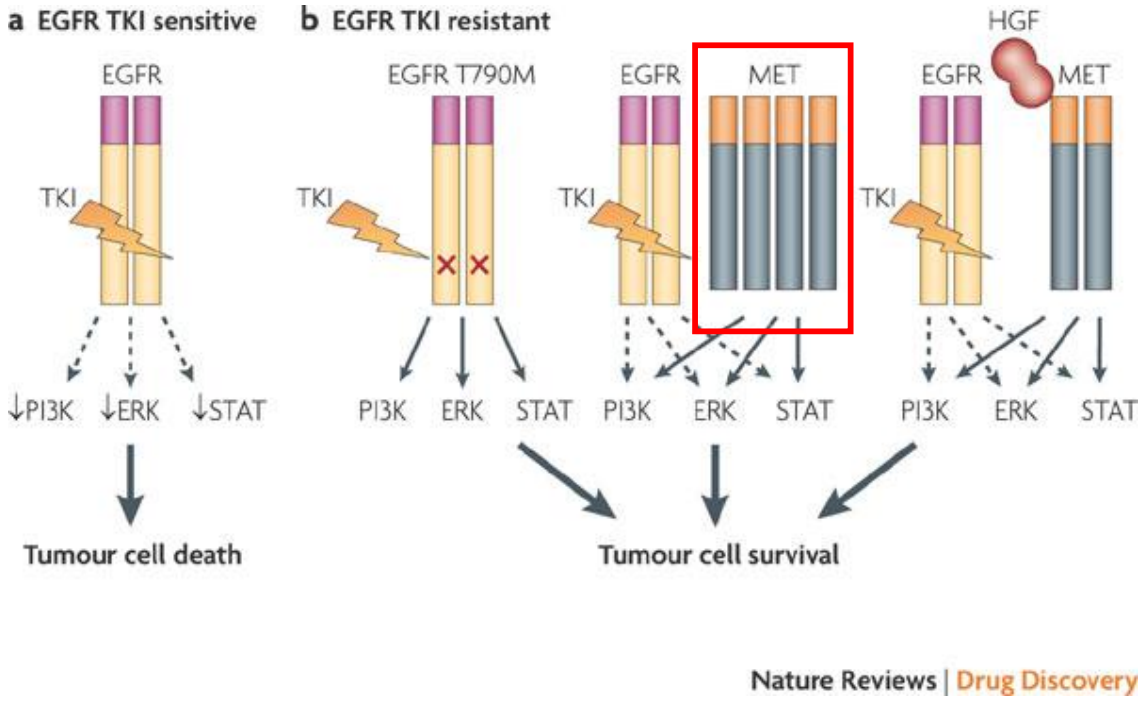
TARGET human gene that **contributes to a disease phenotype and can be targeted directly by a drug (small molecule, monoclonal antibody, …)**



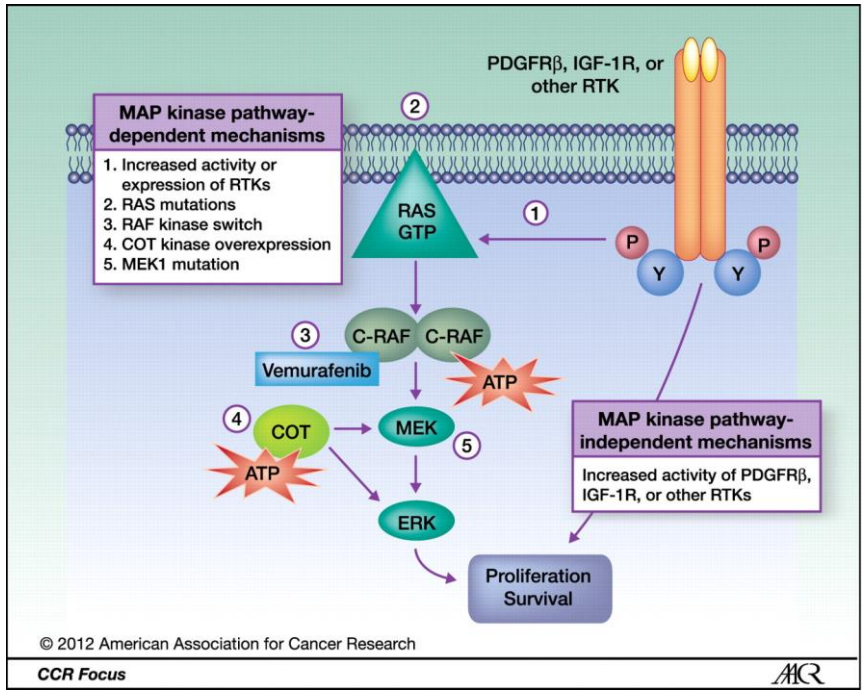
Target & marker genes

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



Sensitivity vs Resistance



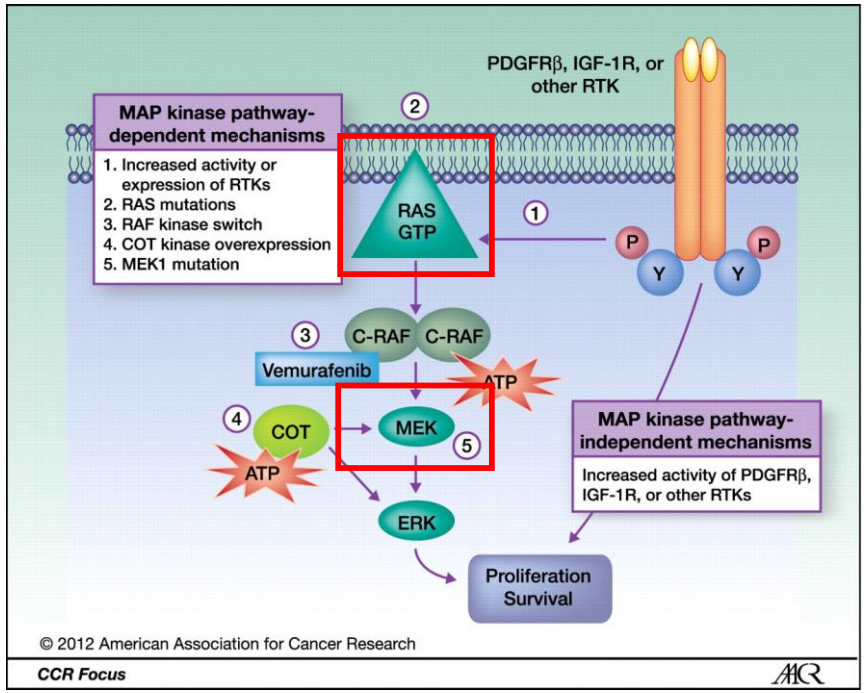
Melanoma treatment with BRAF mutation

VEMURAFENIB

GEMCITABINE

Advanced or metastatic pancreatic cancer

Sensitivity vs Resistance



Melanoma treatment with BRAF mutation

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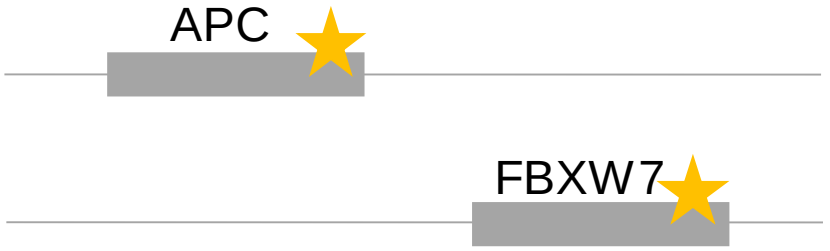
GEM BINE

Advanced or metastatic pancreatic cancer



Pathways, alteration, drug family

KEGG PATHWAY Database

Pathways in which gene is involved

ALTERATION TYPE

Extracted from several sources

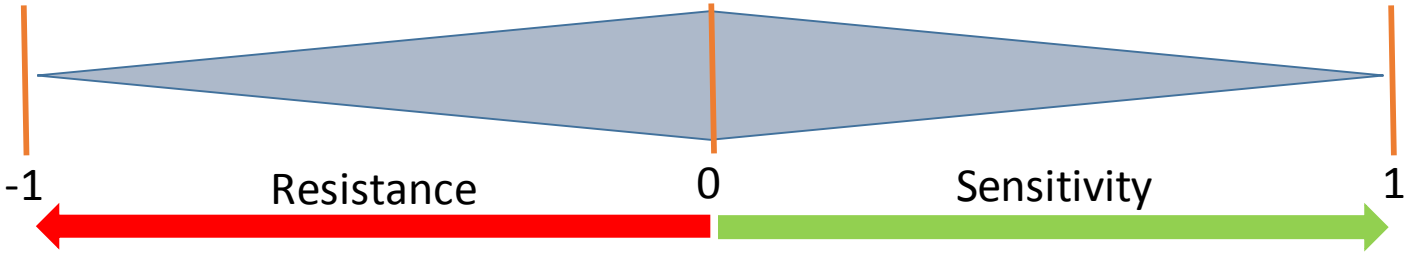
Missense mutation
Amplification
Deletion
Gene fusion

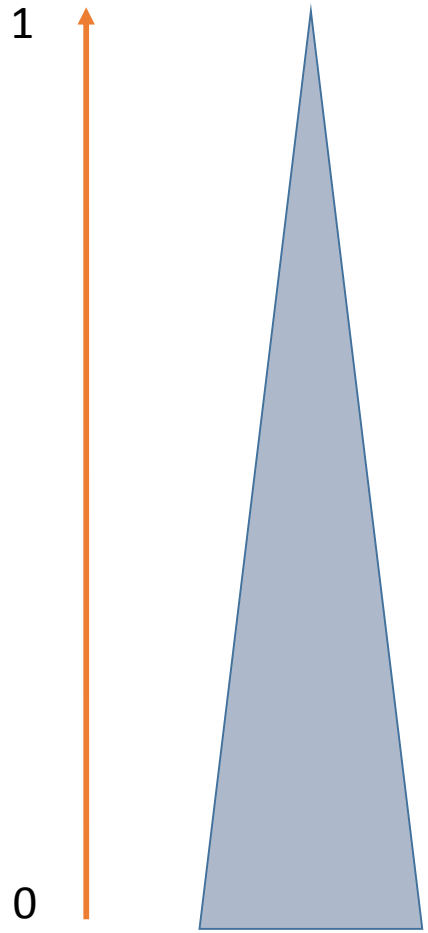
FAMILY DRUG NAME

Target-based classification of drugs

Hydrolases Inhibitor
Cellular antigens Antagonist
Class I cytokines Inhibitor
Epithelial and related channels blocker
Nucleic acid Inhibitor
Receptor tyrosine kinase Agonist
Serine/threonine protein kinases: AGC group Inhibitor
TNF family Monoclonal antibody
Transferases Inhibitor
…

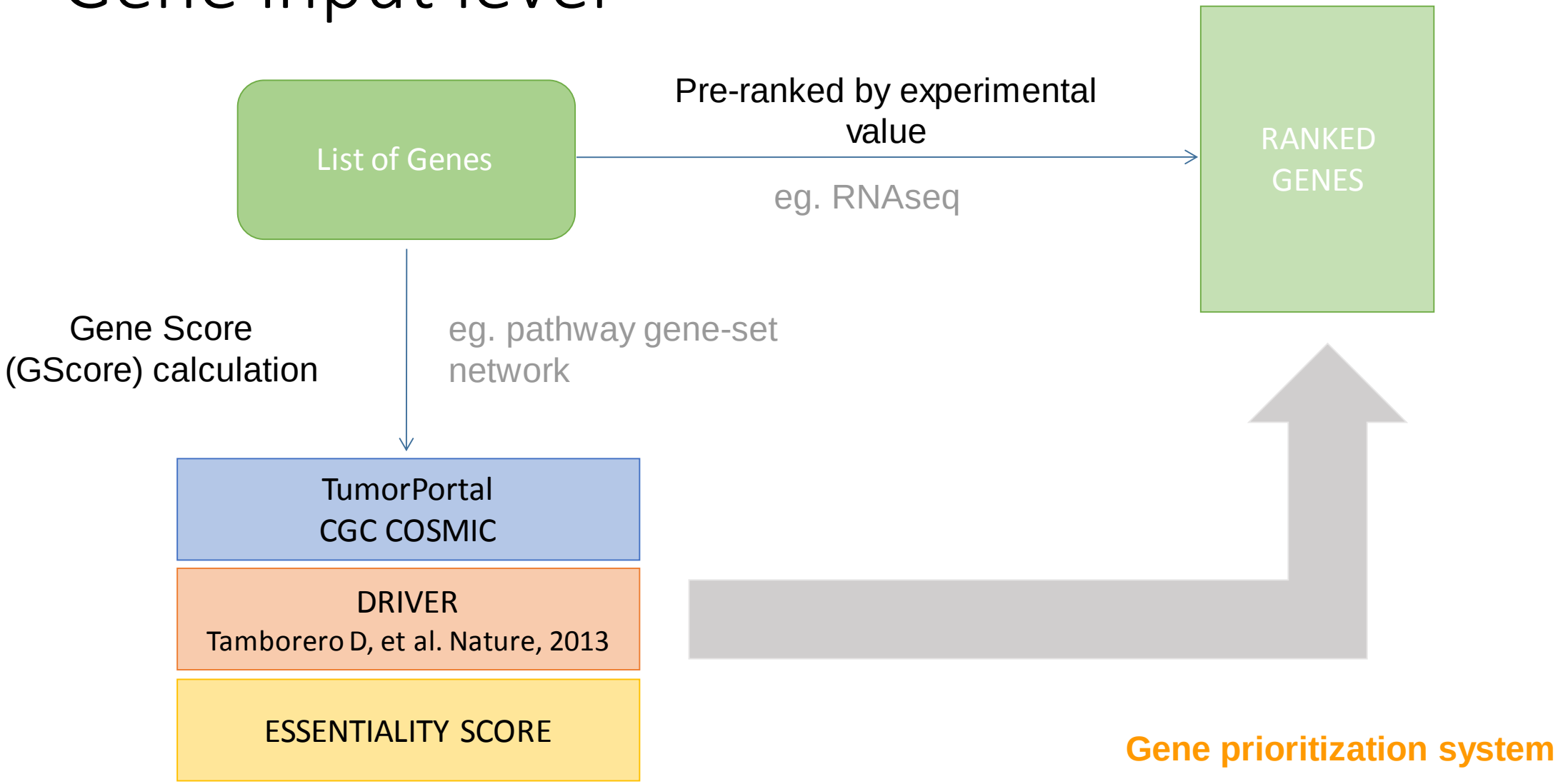
Pre-computed values in PanDrugs





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

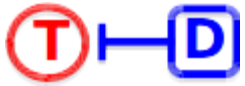
Gene input level



Indirect associations

DRUG-GENE DIRECT ASSOCIATIONS

The altered gene is the target or biomarker of the drug



DRUG-GENE INDIRECT ASSOCIATIONS

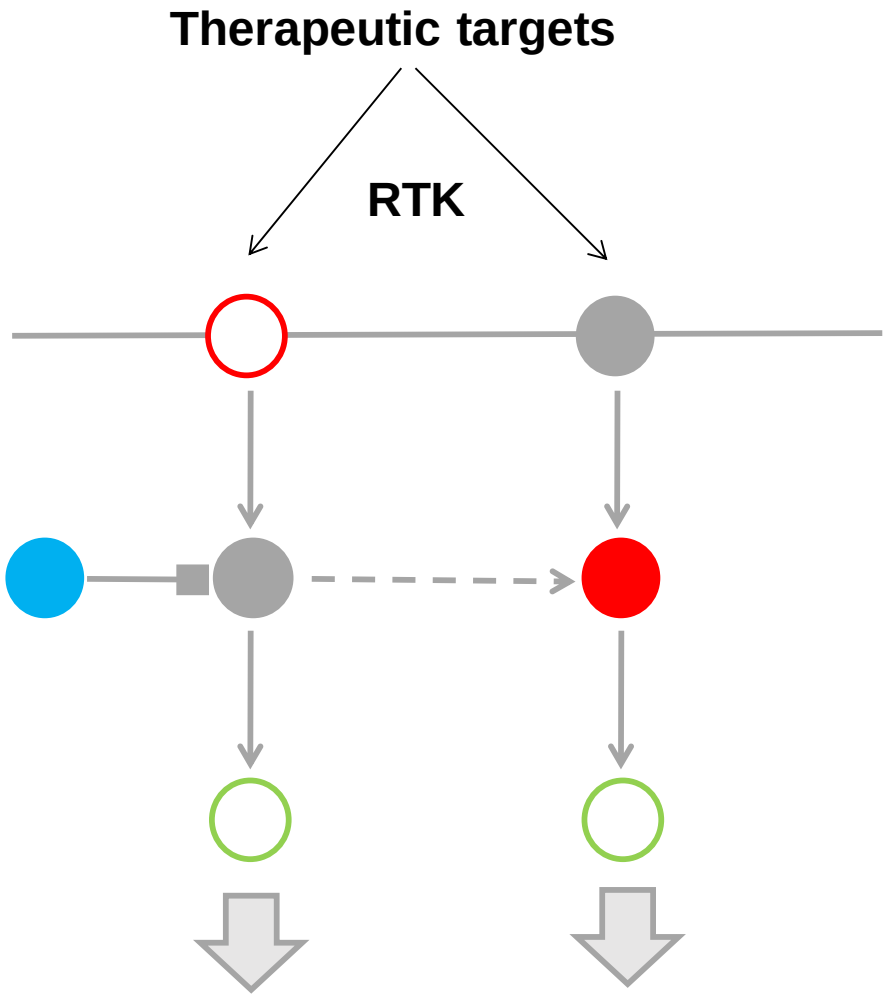
The drug has as a target a gene related to the altered one

D Drug

T Altered target gene

G Altered non target gene

T Wild type target gene



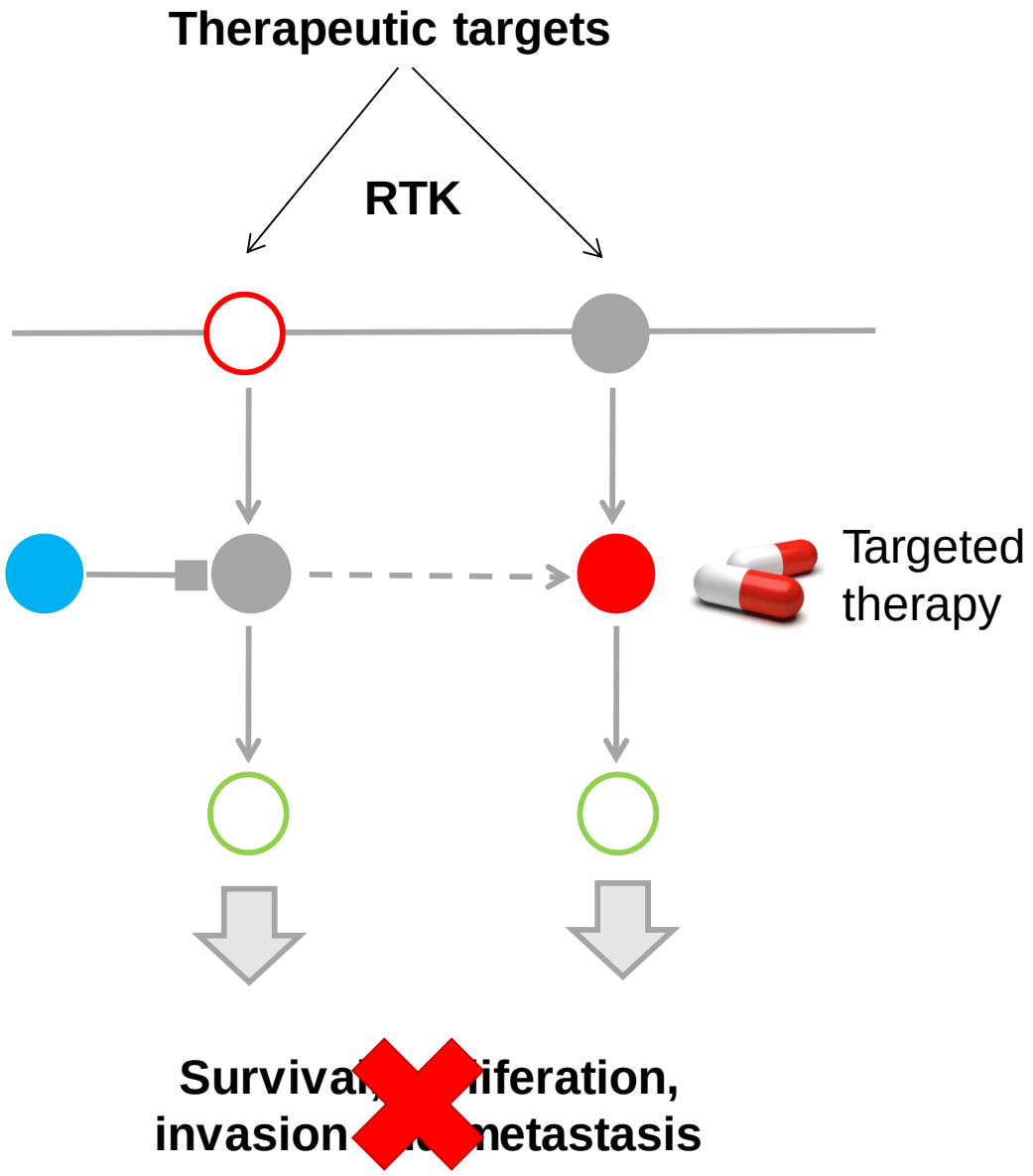
Actionable

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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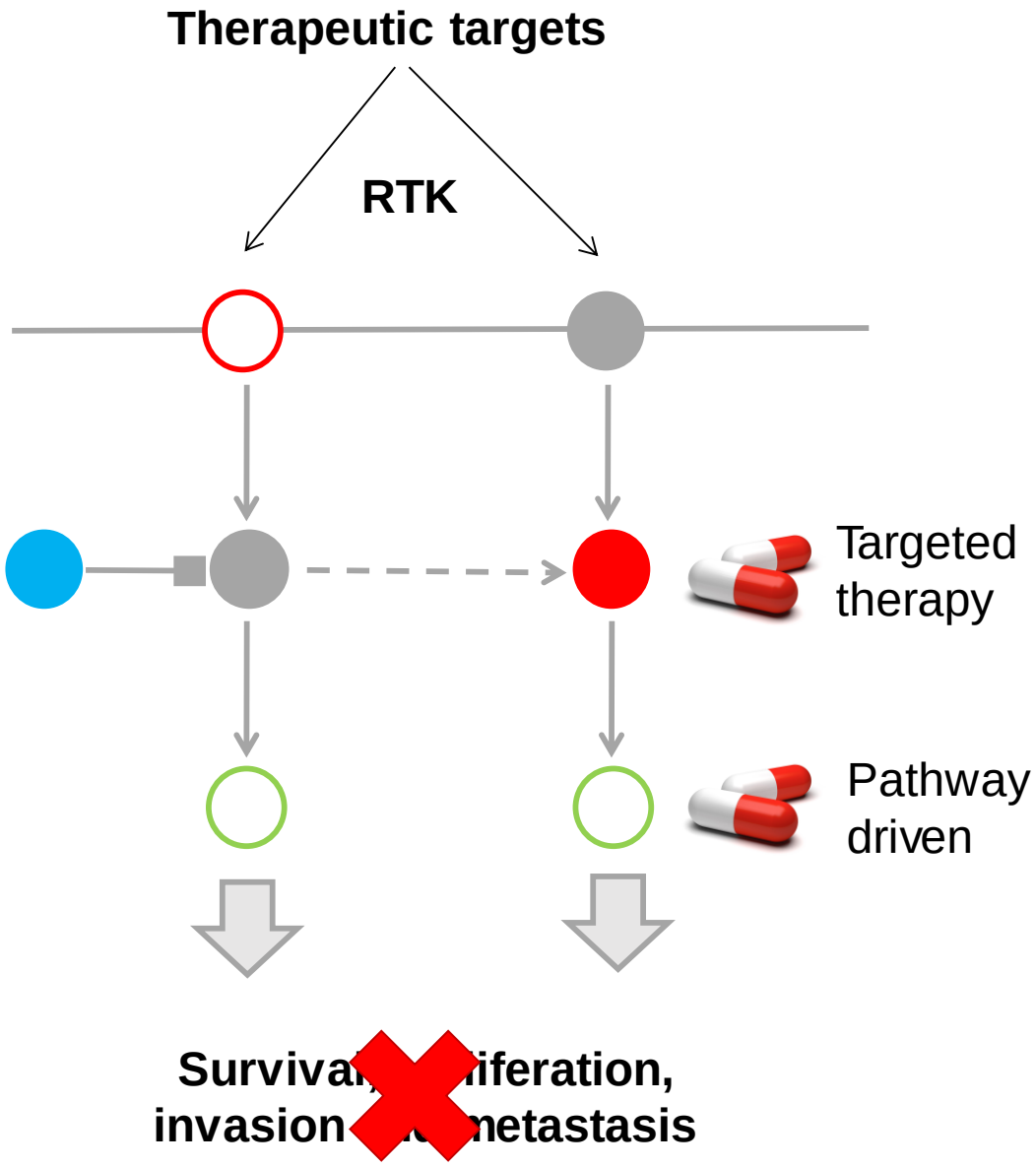
Druggable

1 - Direct pharmacological assignation



Actionable

Wild-type or No Actionable

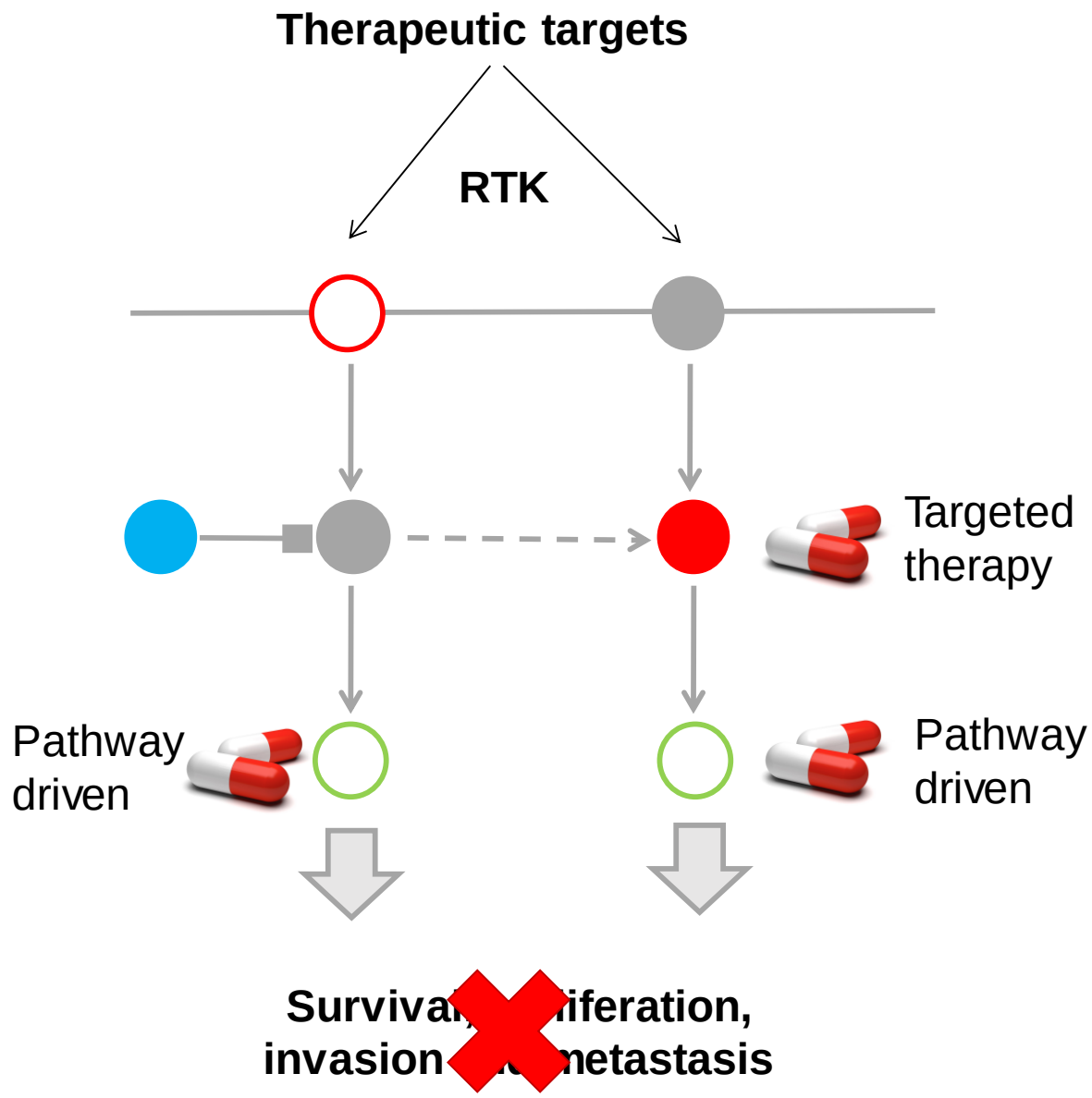
Tumor suppressor gene mutated

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 score (DSCORE) recalculation

Approved and Clinical trials:

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

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

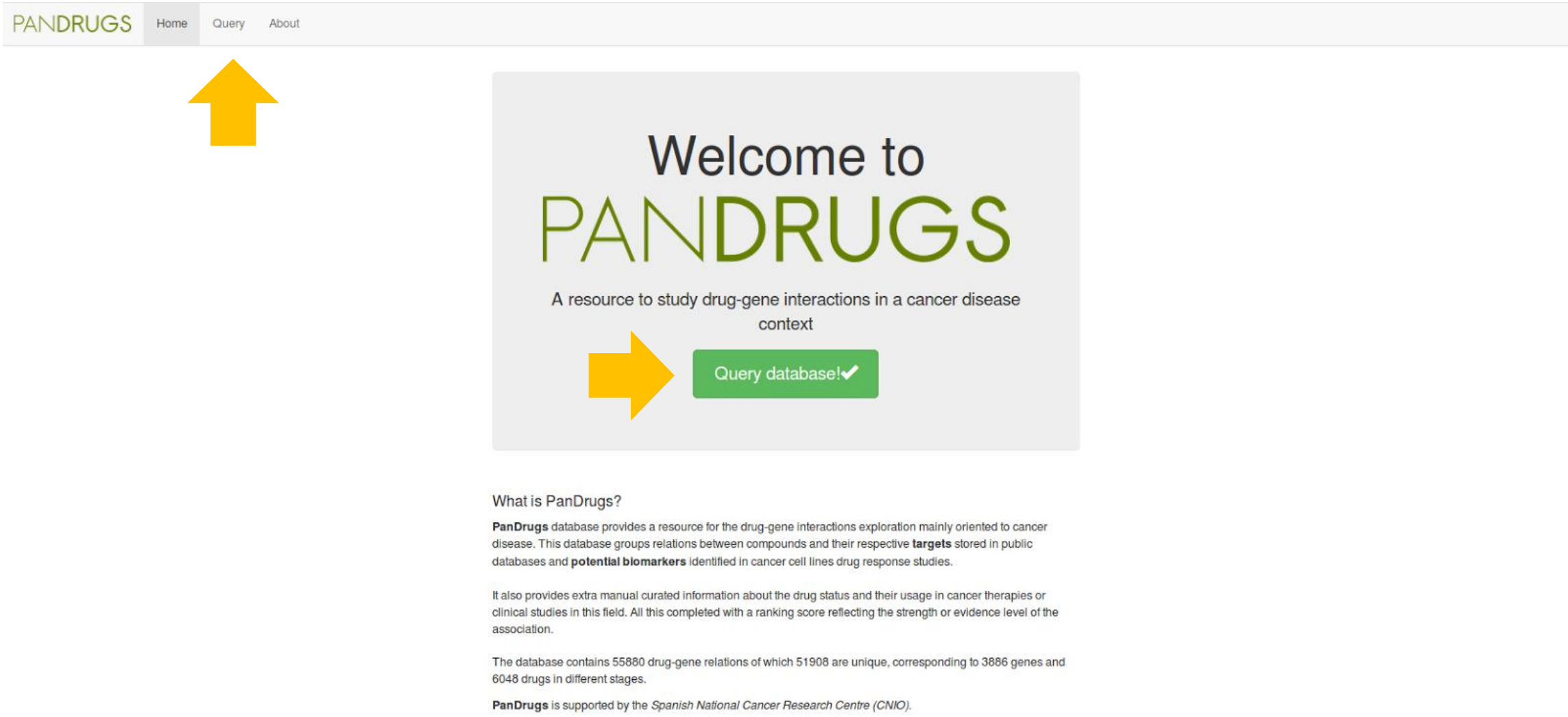
Experimental:

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

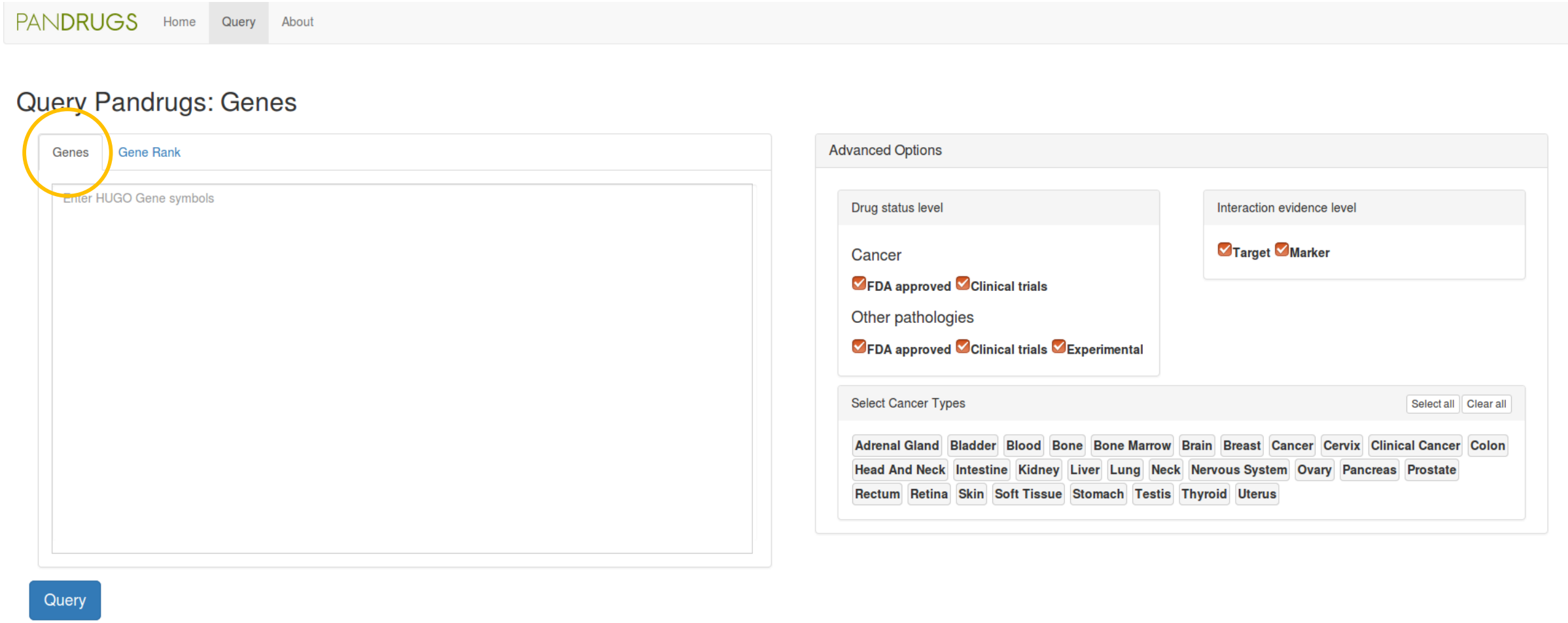
INDIRECT assignations will have a lower DScore unless a marker evidence supports the association.

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.

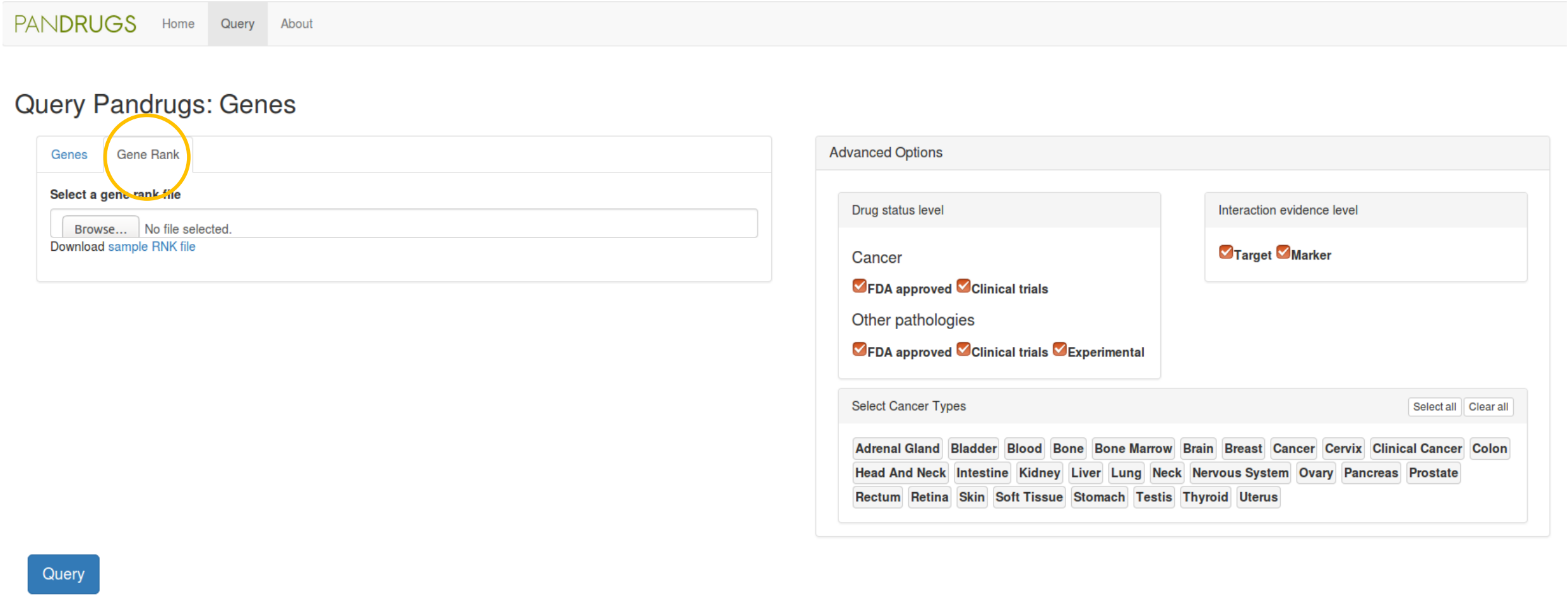
Gene search example



Gene search example



Gene search example



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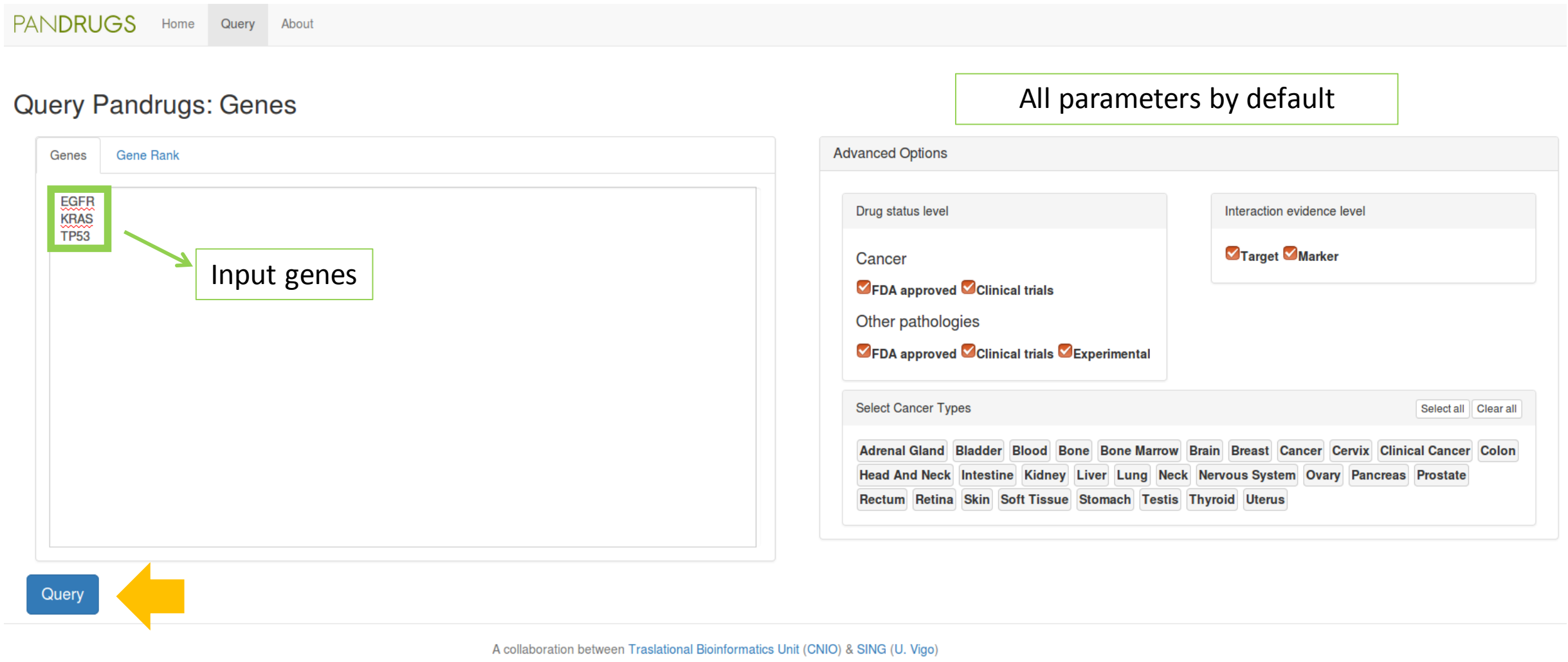

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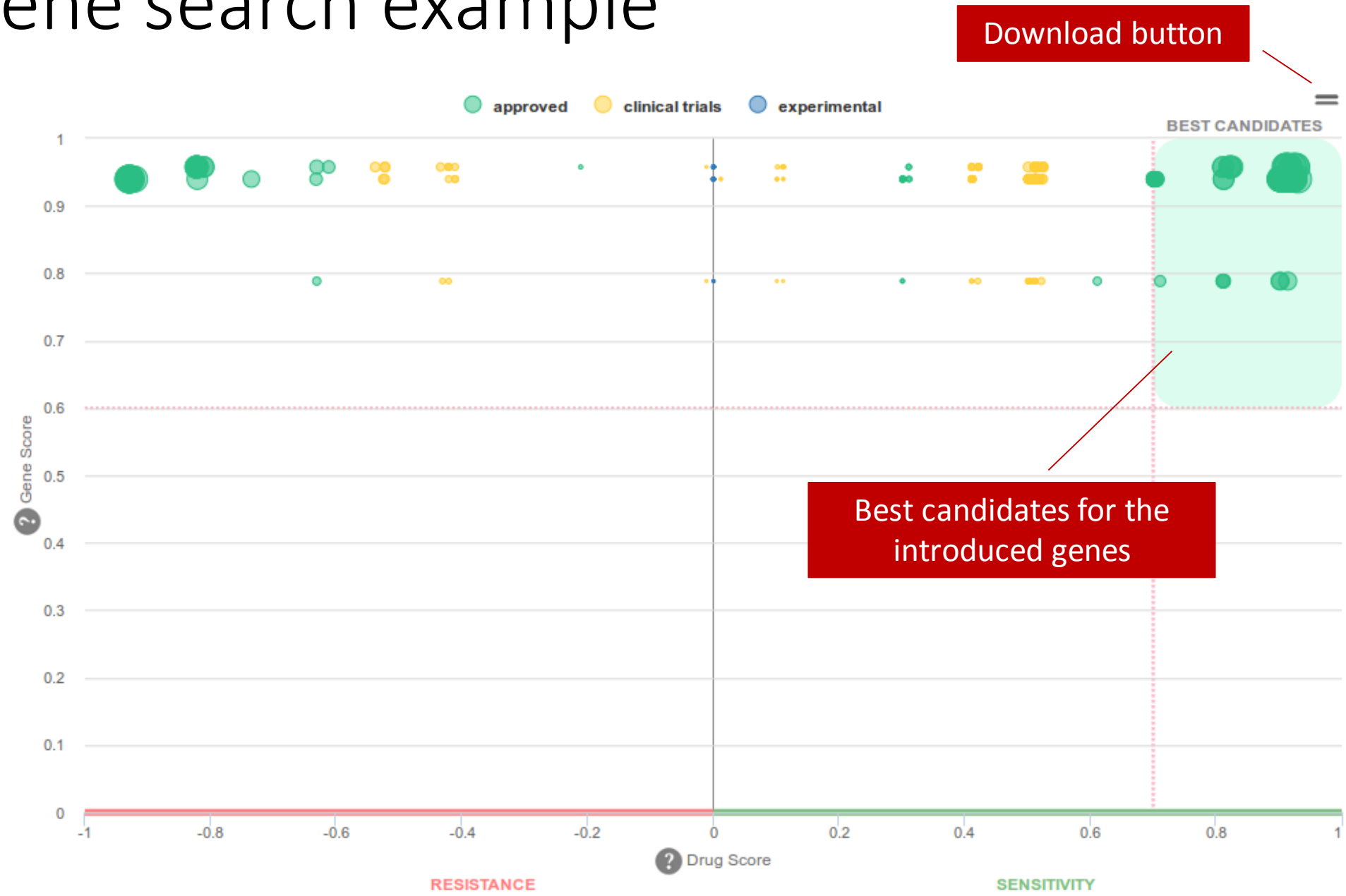

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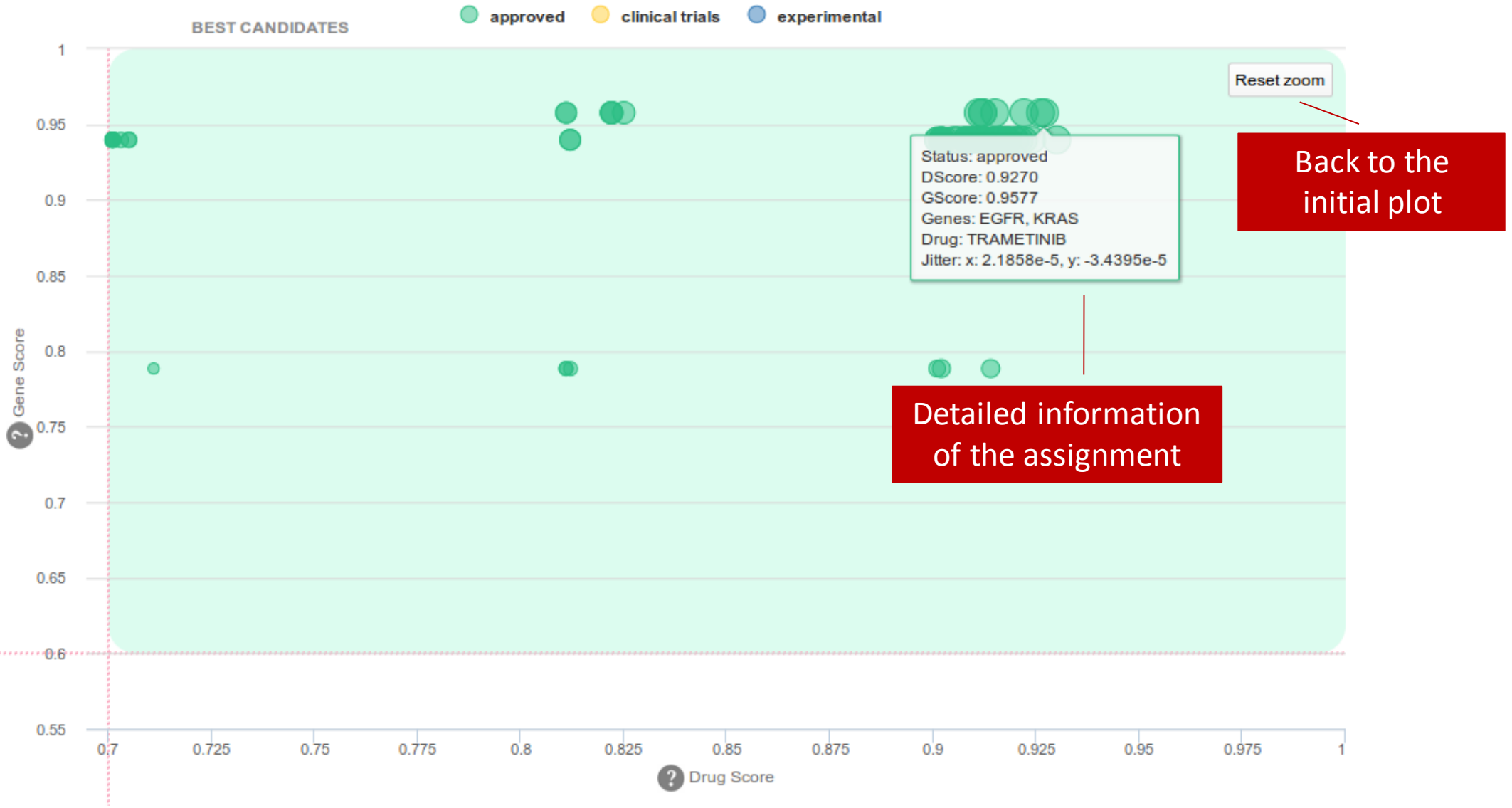

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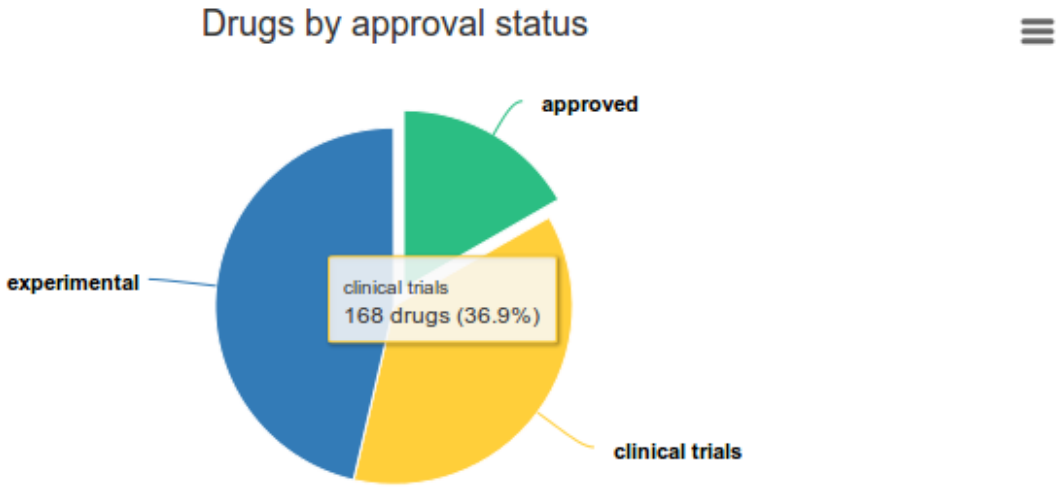

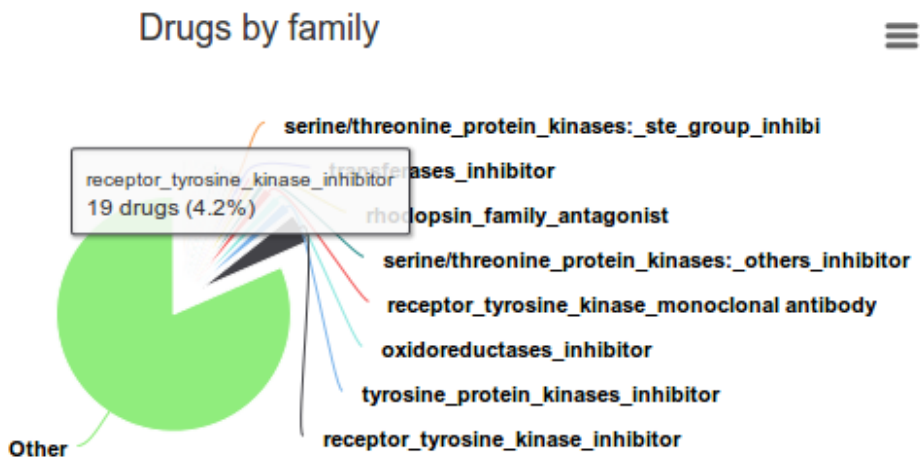

Gene search example

Download as CSV

Actions	Gene(s)	Drug	Family	Source(s)	Drug status	Type of therapy	Interaction	DScore	GScore
+	KRAS and EGFR	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
+	KRAS and EGFR	TRAMETINIB	serine/threonine_protein_kinases:_ste_group_inhibi	CC CFB DB GtPI MCG MCGCT TALC TCT	Approved for skin cancer	Targeted therapy	T···D	0.9270	0.9577
+	KRAS and EGFR	COBIMETINIB	Other	CC CFB DB MCG MCGCT TALC TCT	Approved for skin cancer	Targeted therapy	T···D	0.9260	0.9577
+	KRAS and EGFR	REGORAFENIB	receptor_tyrosine_kinase_inhibitor	DB GtPI MCG MCGCT	Approved for colon, intestine, rectum and stomach cancer	Targeted therapy	T···D	0.9240	0.9577
+	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	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
+	KRAS and EGFR	SORAFENIB	receptor_tyrosine_kinase_inhibitor	CIV CFCT DoCM DB MCG MCGCT PGKB TALC TCGA TEND TTD TCT	Approved for kidney cancer	Targeted therapy	G→T–D	0.9180	0.9577
+	EGFR	PERTUZUMAB	receptor_tyrosine_kinase_monoclonal antibody	CFB DB GtPI MCG PGKB TALC TCGA TTD TCT moAb	Approved for breast cancer	Targeted therapy	T–D	0.9180	0.9398
+	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

−	KRAS and EGFR	TRAMETINIB	serine/threonine_protein_kinases:_ste_group_inhibi	CC CFB DB GtPI MCG MCGCT TALC TCT	Approved for skin cancer	Targeted therapy	T···D	0.9270	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_inhibi	CancerCommons, DrugBank, GuideToPharmacologyInteractions, MyCancerGenome, MyCancerGenomeClinicalTrial, TALC, TdgClinicalTrial			G→T–D	0.9270	0.9577
	Molecular alterations in KRAS are associated to 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_inhibi	ClearityFoundationBiomarkers			T···D	0.8220	0.9577

THE END

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