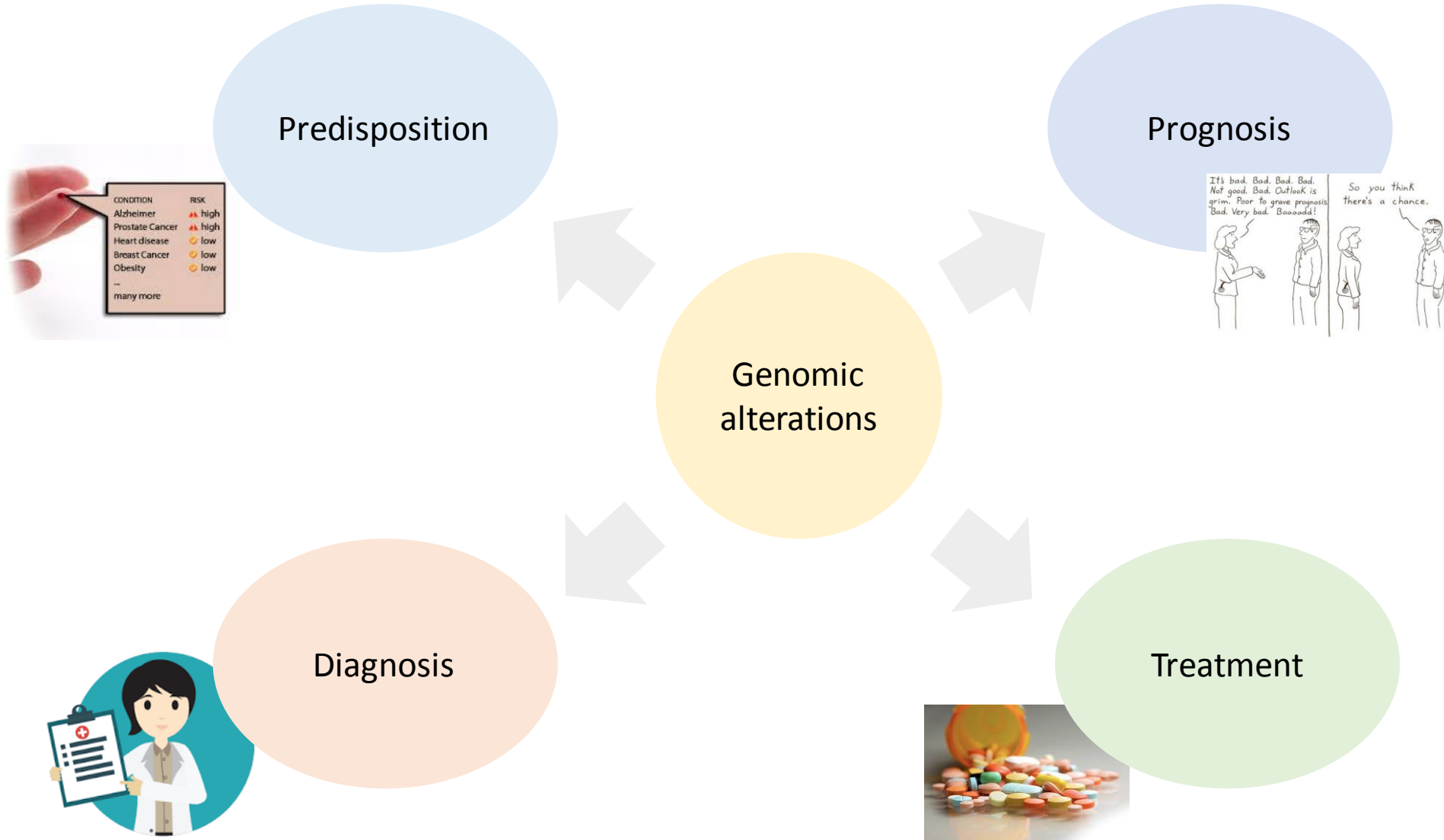


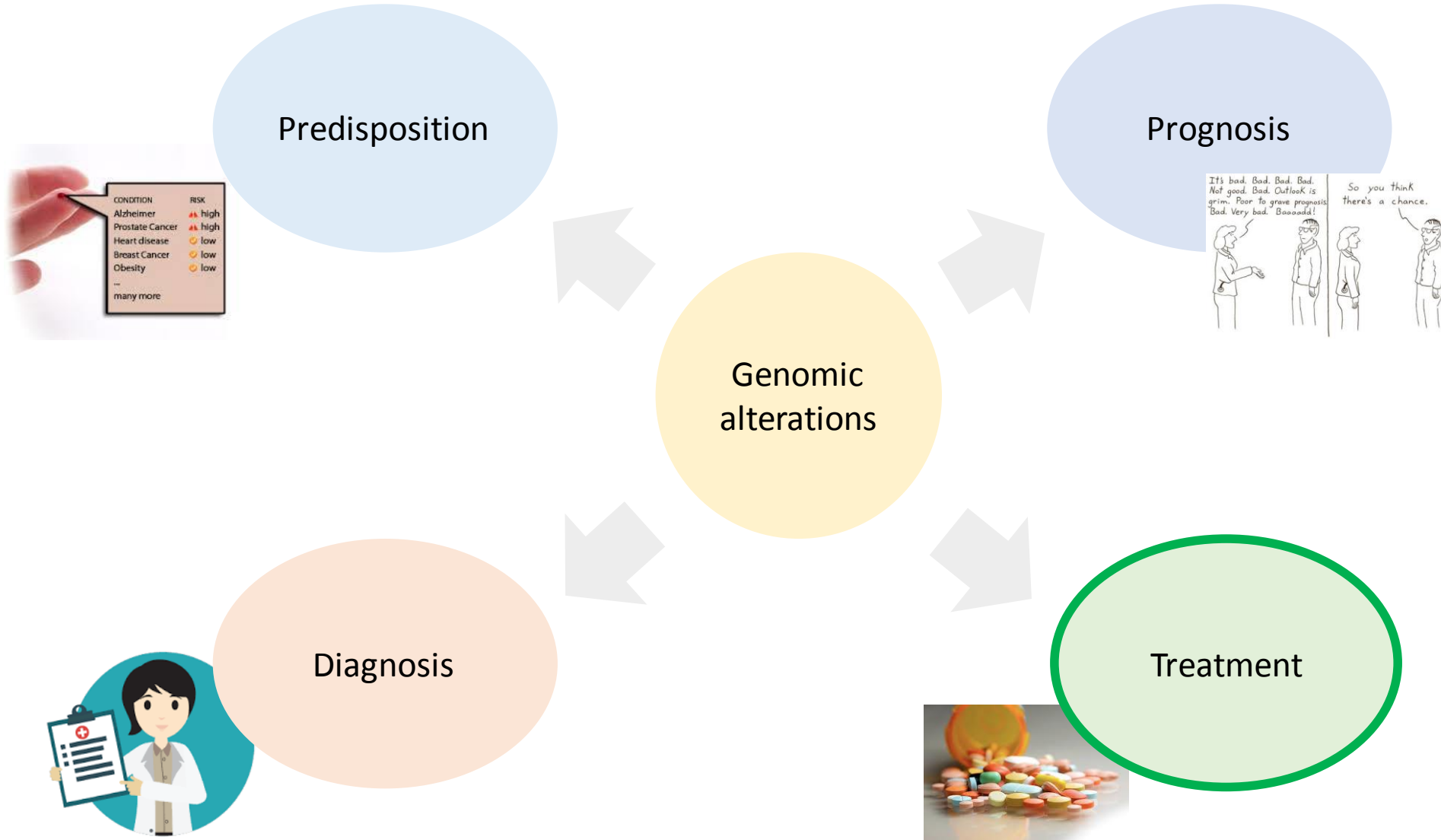
Precision medicine: NGS variant analysis and interpretation for translational research

PanDrugs: Matching mutations with therapies

Fátima Al-Shahrour ● Javier Perales ● Elena Piñeiro

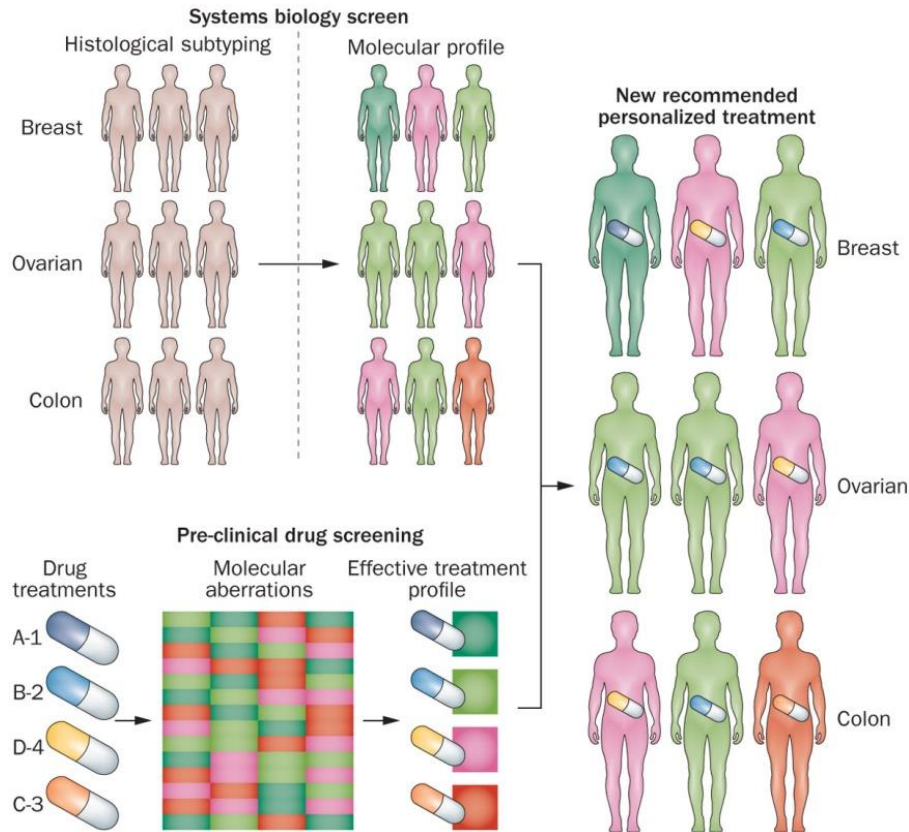
September 29, 2016





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

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 assignments according to their therapeutic utility in a specific genomic context.

Web page

PANDRUGS Home Query About

Welcome to PANDRUGS

A resource to study drug-gene interactions in a cancer disease context

Query database! ✓


What is PanDrugs?

PanDrugs database provides a resource for the drug-gene interactions exploration mainly oriented to cancer disease. This database groups relations between compounds and their respective **targets** stored in public databases and **potential biomarkers** identified in cancer cell lines drug response studies.

It also provides extra manual curated information about the drug status and their usage in cancer therapies or clinical studies in this field. All this completed with a ranking score reflecting the strength or evidence level of the association.

The database contains 55880 drug-gene relations of which 51908 are unique, corresponding to 3886 genes and 6048 drugs in different stages.

PanDrugs is supported by the *Spanish National Cancer Research Centre (CNIO)*.



A word cloud containing various drug names and identifiers such as GW843682X, BRD6368, NSC 95397, BRD9876, NUTLIN-3, ABT-737, PD-157695, NAVITOCILAX, RAC1 INHIBITOR, ZEBULARIN, TG101348, SIROLIMUS, BIX-01294, BORTEZOMIB, TELOMERASE INHIBITOR, IXETOPOSIDE, NEOPENITOLIDE, CYTOCHALASIN, BFQI-1, PARTHENOLIDE, SEPANTRONIUM, BROMIDE, PIPERLONGUMIN, EMERCK60, 2-AMINO-3-CHLORO-1,4-NAPHTHOQUINONE, 2-(SEC-BUTYLDISULFANYL)-1H-IMIDAZOLE, CHEMBL254381, LY2183240, BMS-536924, SELUMETINIB, KINETIN, RIBOSIDE, IDARUBICIN, TIPIFARNIB, P2NSC632839, 79966-13-5, PARBENDAZOLE, GTPL7016, NSC 652287, URACILIC ACID, INDISULAM, EVODIAMINE, PAC-1, TOZASERTIB, AT-101, GMX-1778, SN-38, and SERDEMETAN.

A collaboration between Traslational Bioinformatics Unit (CNIO) & SING (U. Vigo)



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




Next Generation Computer Systems Group
Sistemas Informáticos de Nueva Generación

Sources




Cancer Commons
CIViC
The Clarity 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



TARGET
(Tumor Alterations
Relevant for Genomics
driven Therapy)

Drug-gene interactions


Van Allen et al. (2014) Nat Med



**Genomics of Drug
Sensitivity in Cancer**

Drug-gene interactions based on CCL
studies

Iorio F et al. (2016) Cell

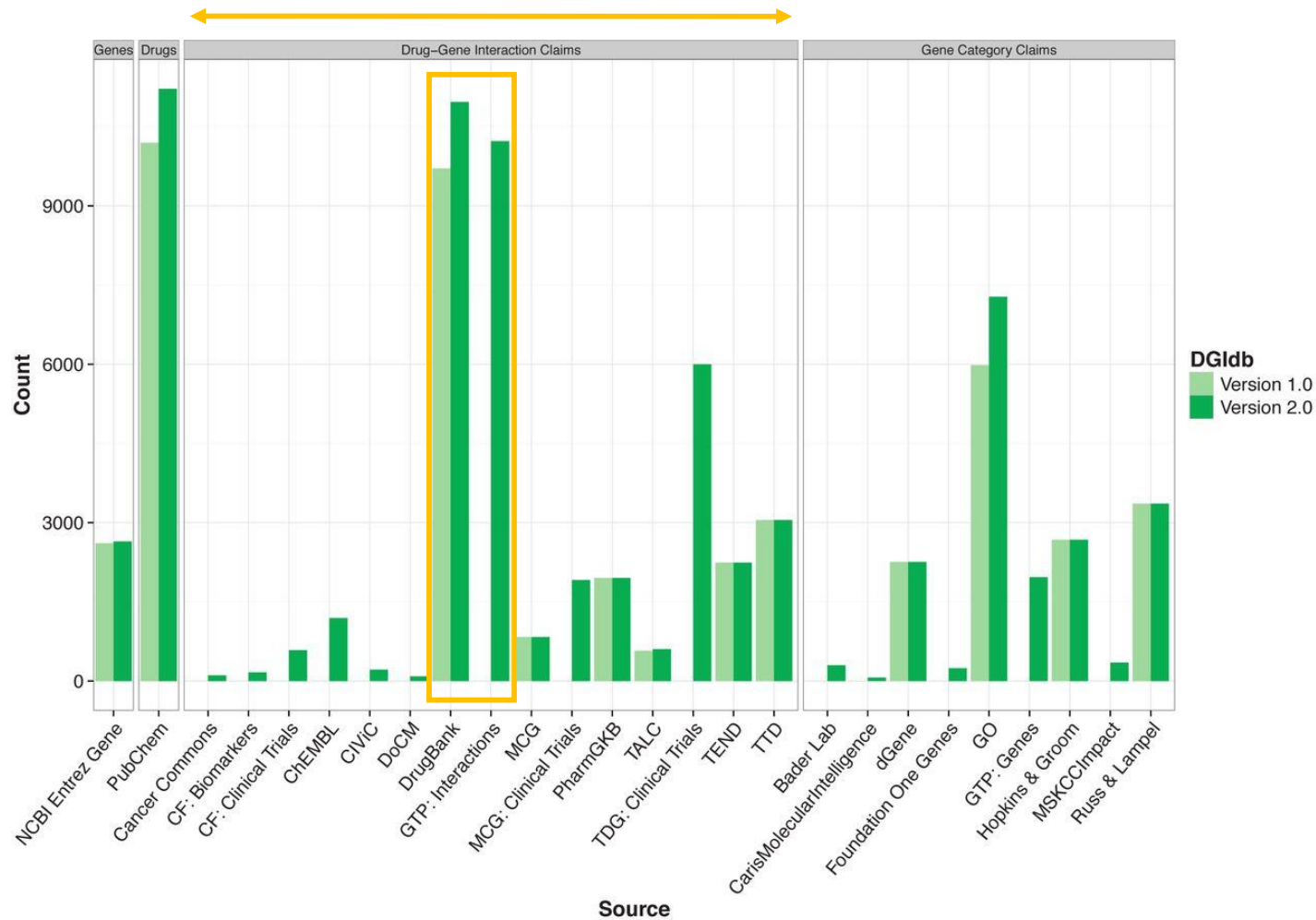


Cancer Therapeutics Response Portal

Drug-gene interactions based on CCL
studies

Rees et al. (2016) Nat Chem Biol

DGIdb



Cancer Commons: drugs approved or undergoing clinical trials for use in lung, prostate and skin cancer

Clarity Foundation Biomarkers: biomarkers that predict response to selected drugs in ovarian tumors

Clarity 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)

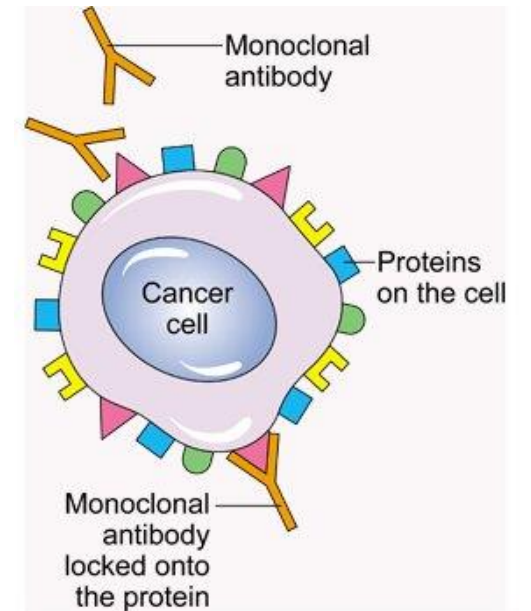


Diagram showing a monoclonal antibody attached to a cancer cell
© CancerHelp UK

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

The screenshot shows the TARGET database website. On the left is a sidebar with the CGA logo and a list of tools including Home, Help Forum, ABSOLUTE, ChainFinder, BreakPointer, Copynumber Pipeline, ContEst, dRanger, D-ToxoG, Firehose, GISTIC, HAPSEG, Indelocator, InVEx, JuncBASE, MuTest, and MutSig. The main content area has a 'Home' breadcrumb, a 'TARGET' title, and a 'What is TARGET?' section. This section defines TARGET as a database of genes linked to clinical actions and provides a description of its purpose. Below this is a 'How do I get the TARGET database?' section with links to three Excel spreadsheets. To the right of these links is a text block in orange asking for specific drug name information and listing three types of data: sensitivity/resistance, target/marker gene, and genomic alteration. At the bottom is a 'How can I contribute to the TARGET database?' section with a link to a survey.

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
- MuTest
- 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

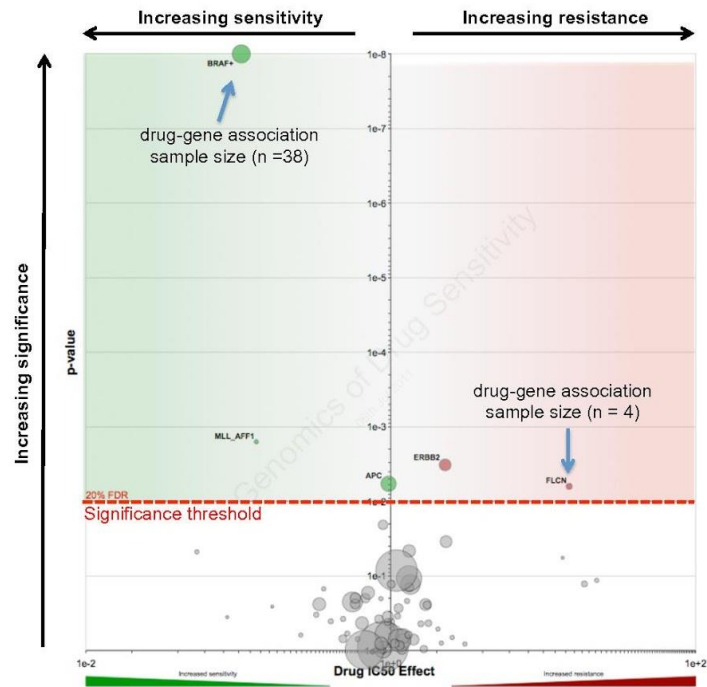
How can I contribute to the TARGET database?

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.

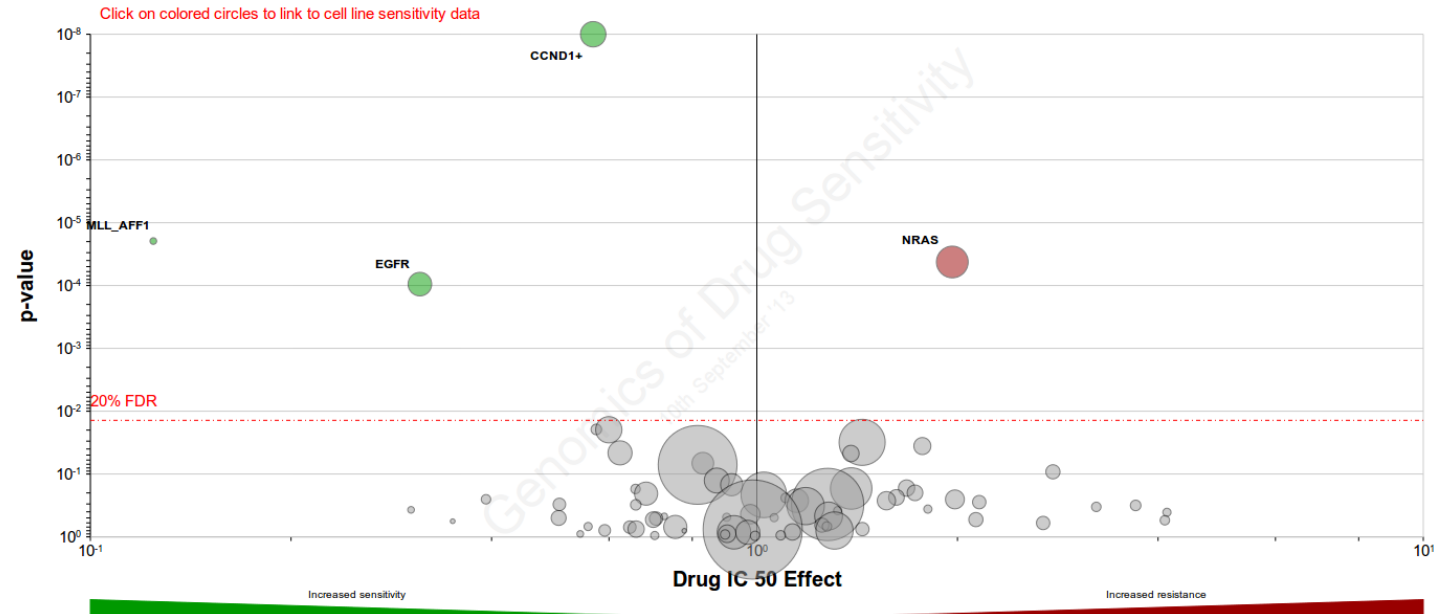
GDSC

~ 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:

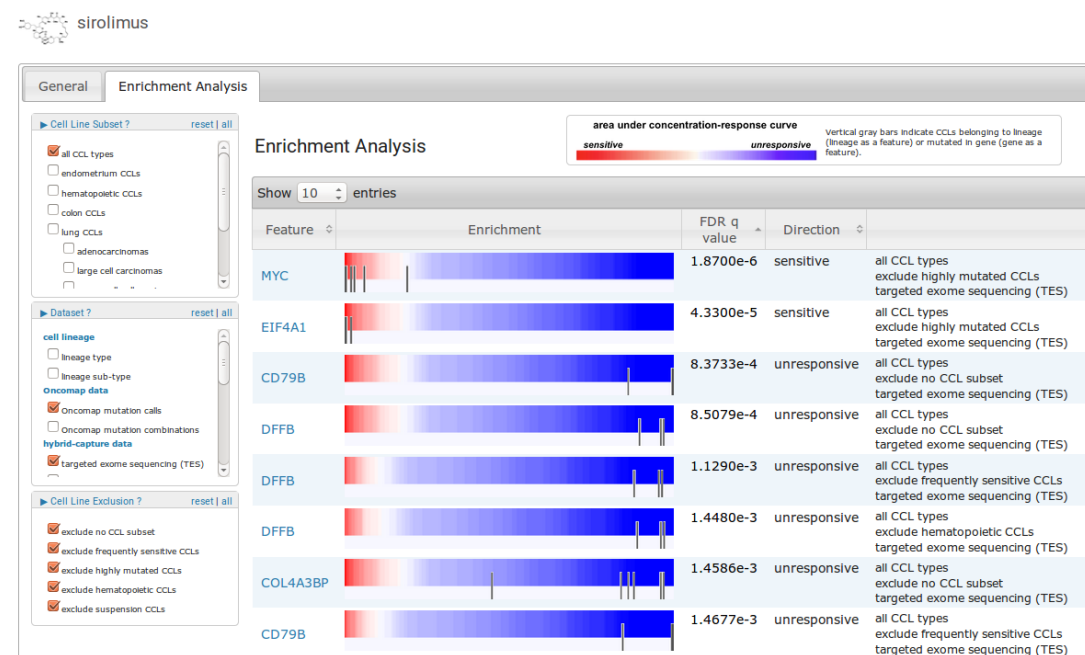
Structure	Name	Synonyms	Targets	Status	starting assay concentration (uM)
	sirolimus	rapamycin;Rapamune	inhibitor of mTOR via FRB domain (in complex with FKBP)	FDA-approved	37

Showing 1 to 1 of 1 entries (filtered from 185 total entries)


[First](#) [Previous](#) [1](#) [Next](#) [Last](#)

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

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




Sources



DGIdb
THE DRUG GENE INTERACTION DATABASE


Cancer Commons
CIViC
The Clarity 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



TARGET
(Tumor Alterations
Relevant for Genomics
driven Therapy)

Drug-gene interactions


Van Allen et al. (2014) Nat Med



**Genomics of Drug
Sensitivity in Cancer**

Drug-gene interactions based on CCL
studies

Iorio F et al. (2016) Cell



Cancer Therapeutics Response Portal

Drug-gene interactions based on CCL
studies

Rees et al. (2016) Nat Chem Biol



ChemSpider
Search and share chemistry



Standardization of the drug name

Approval status

Approved

Tumor type

Cancer clinical trials

Other



Repurposing

Clinical trials

Cancer clinical trials

Other



Repurposing

Experimental

Withdrawn

Undefined

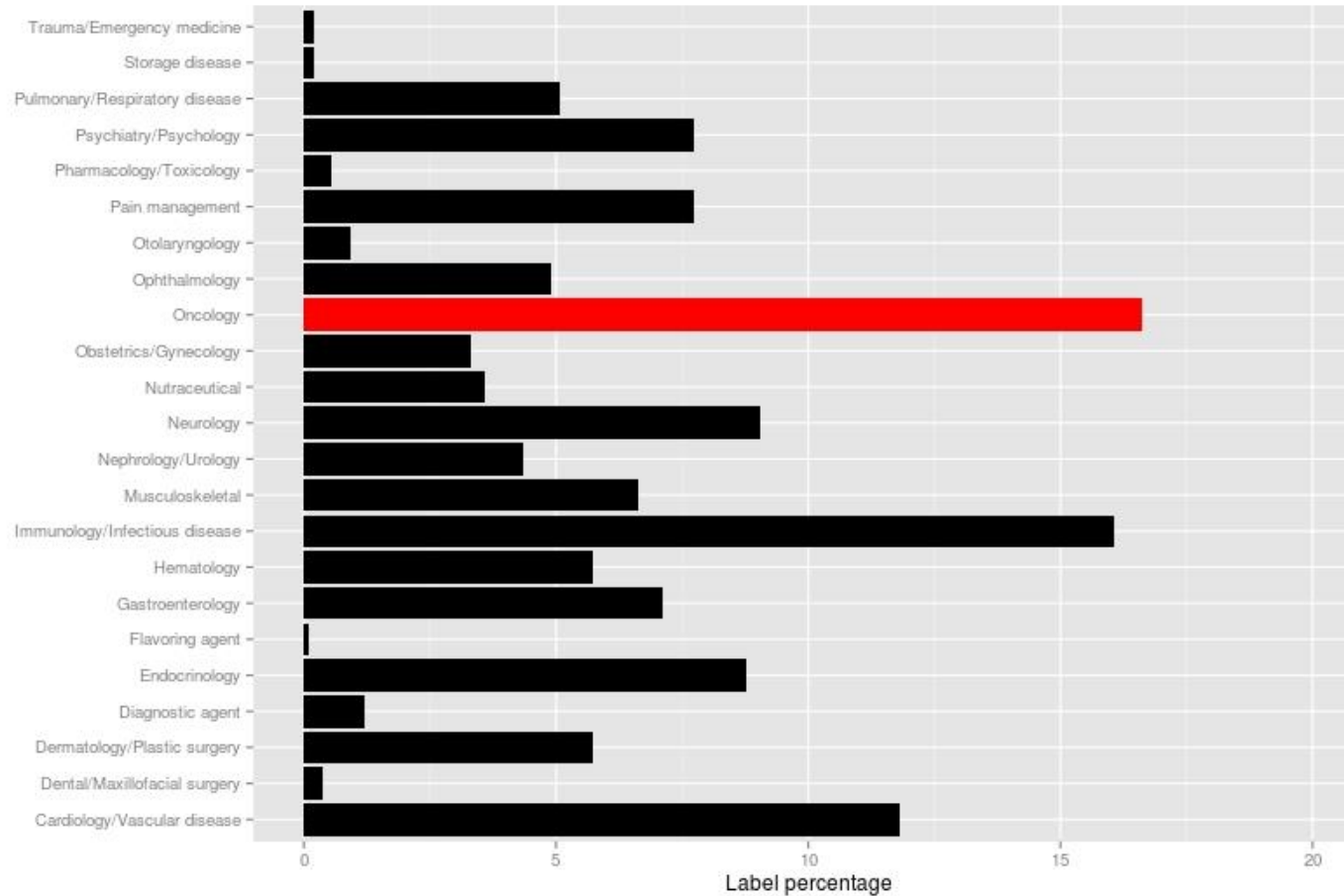


ClinicalTrials.gov

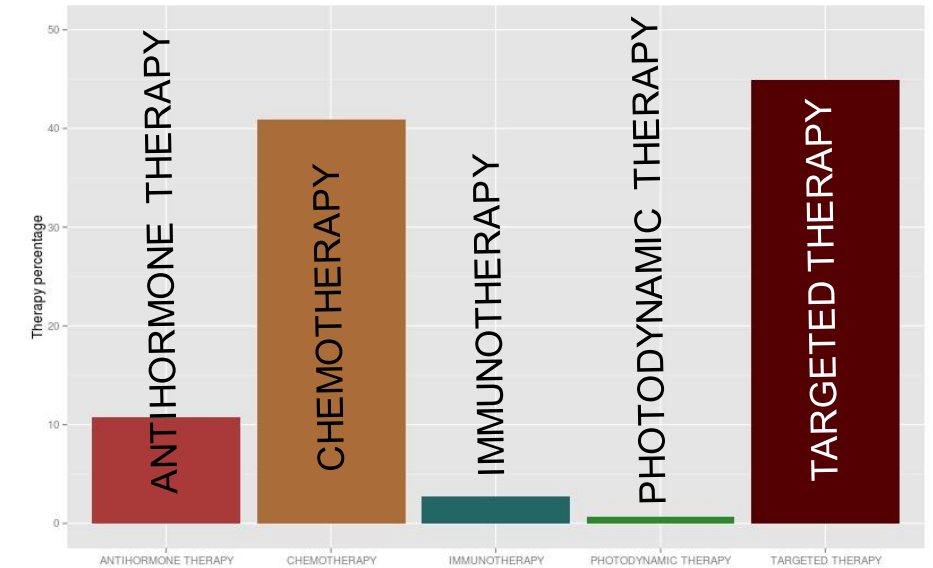
A service of the U.S. National Institutes of Health

Pathological area and cancer therapy type

Distribution of Disease Category Labels in PanDrugs

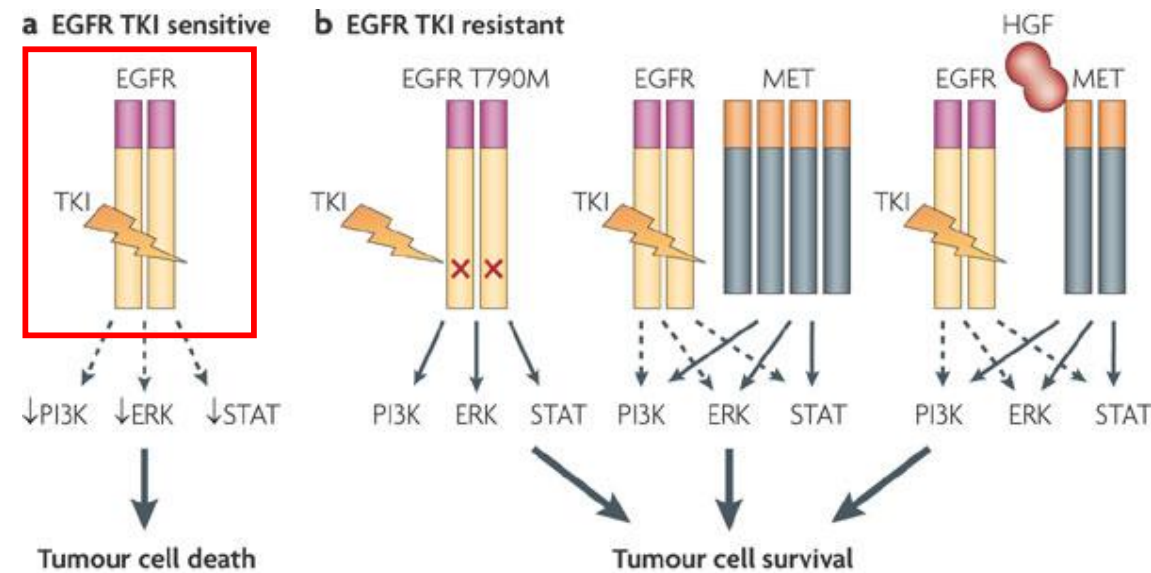


THERAPIES IN ONCOLOGY TREATMENT DRUGS



Target & marker genes

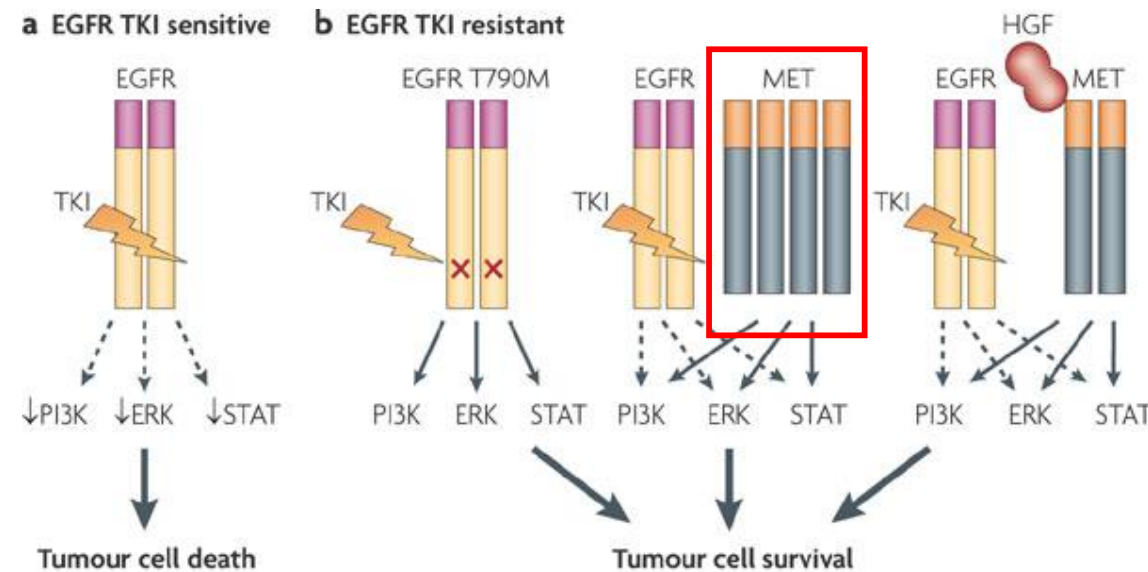
TARGET human gene that **contributes to a disease phenotype** and can be targeted directly by a drug (small molecule, monoclonal antibody, ...)



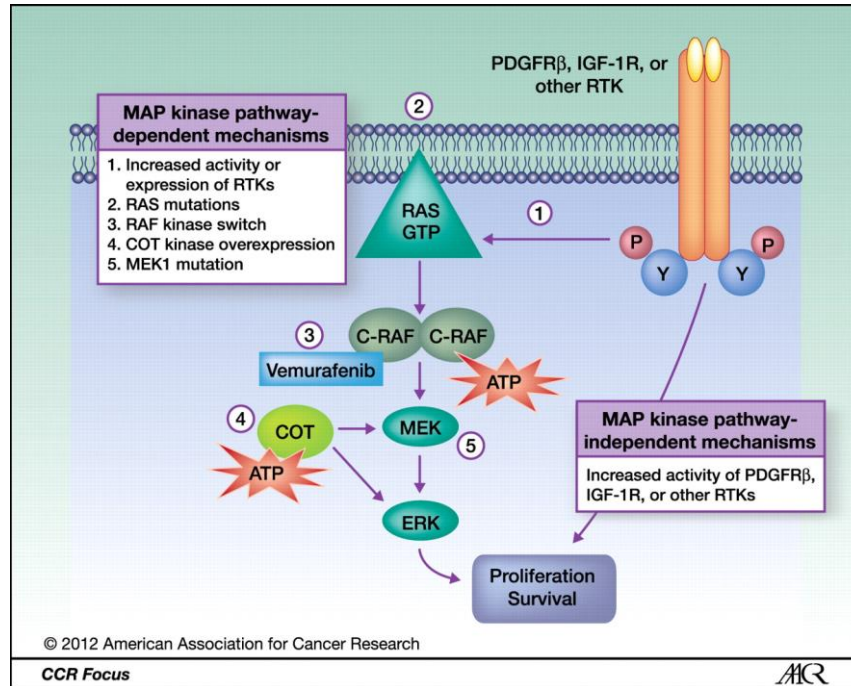
Target & marker genes

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



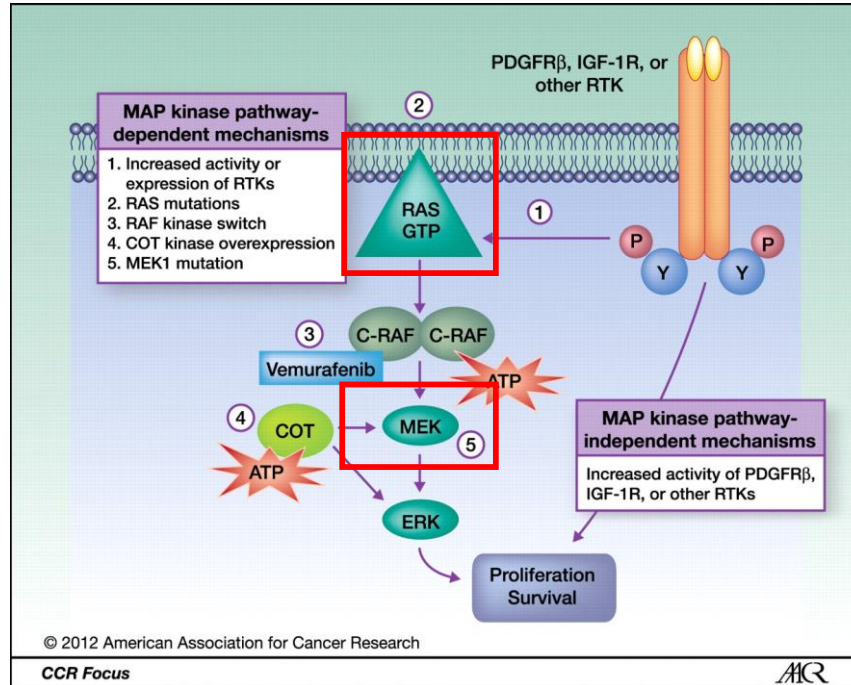
Melanoma treatment with BRAF mutation

VEMURAFENIB



Advanced or metastatic pancreatic cancer

Sensitivity vs Resistance



Melanoma treatment with BRAF mutation

~~VEMURAFENIB~~



Advanced or metastatic pancreatic cancer

APC ★

FBXW7 ★

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

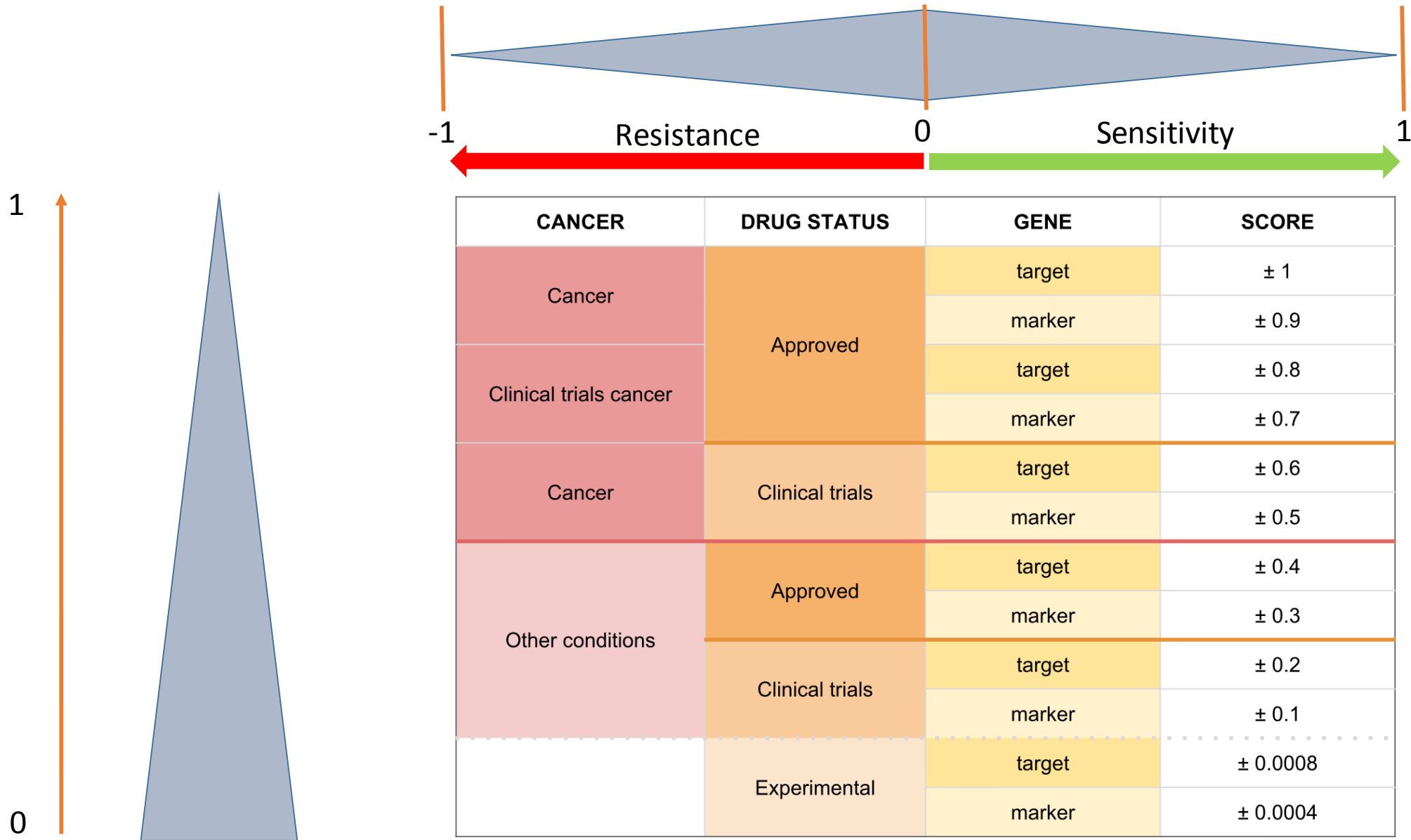
FAMILY DRUG NAME

Target-based classification
of drugs

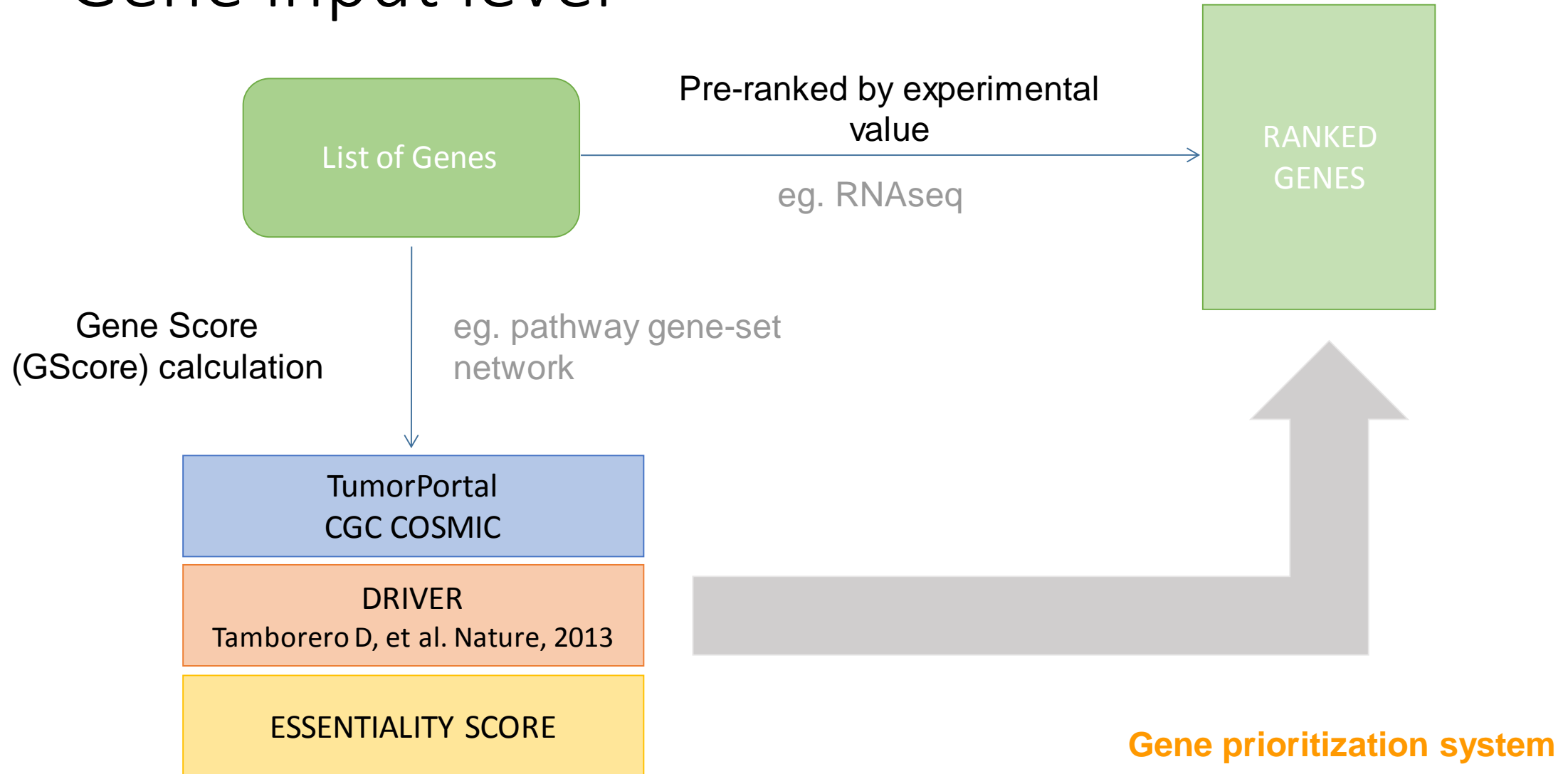
Hydrolases Inhibitor
Cellular antigens Antagonist
Class I cytokines Inhibitor
Epithelial and related channels blocker
Nucleic acid Inhibitor
Receptor tyrosine kinase Agonist
Serine/threonine protein kinases: AGC group Inhibitor
TNF family Monoclonal antibody
Transferases Inhibitor
...



Pre-computed values in PanDrugs



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

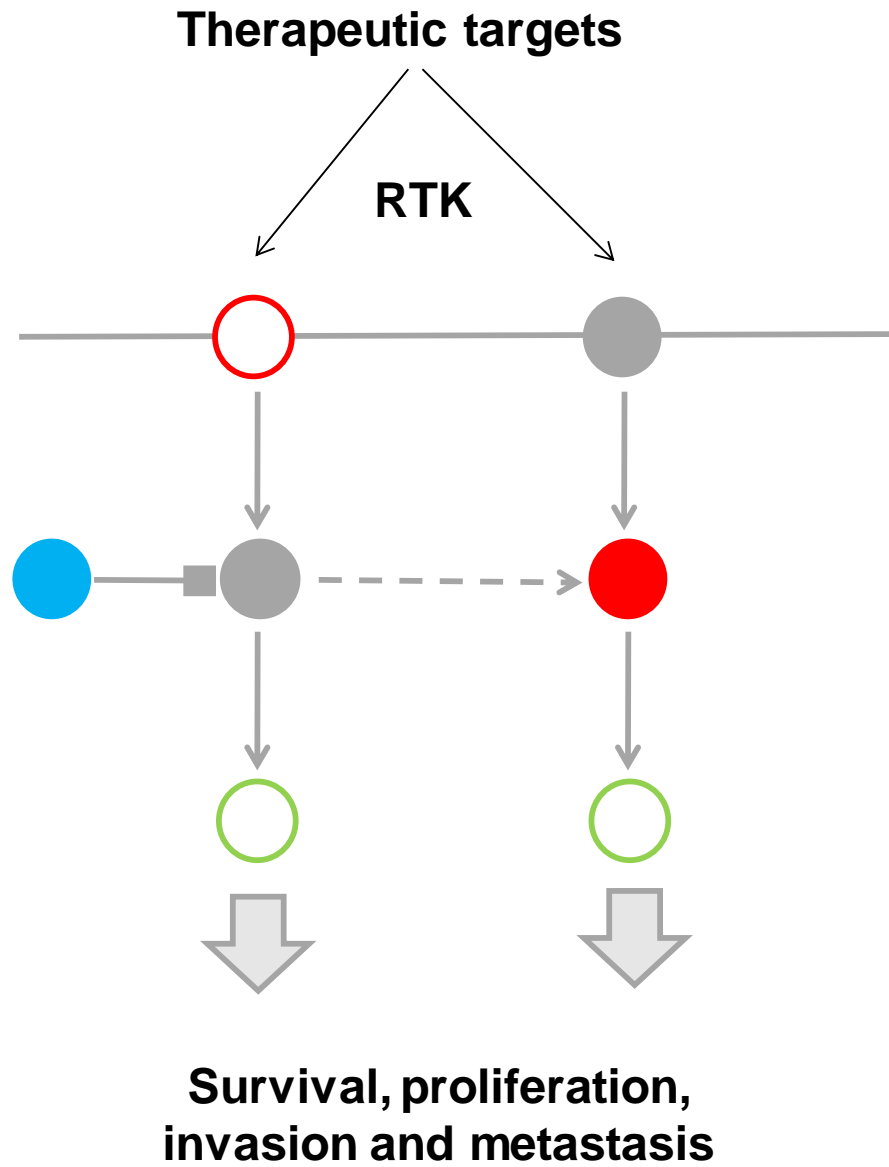




D Drug

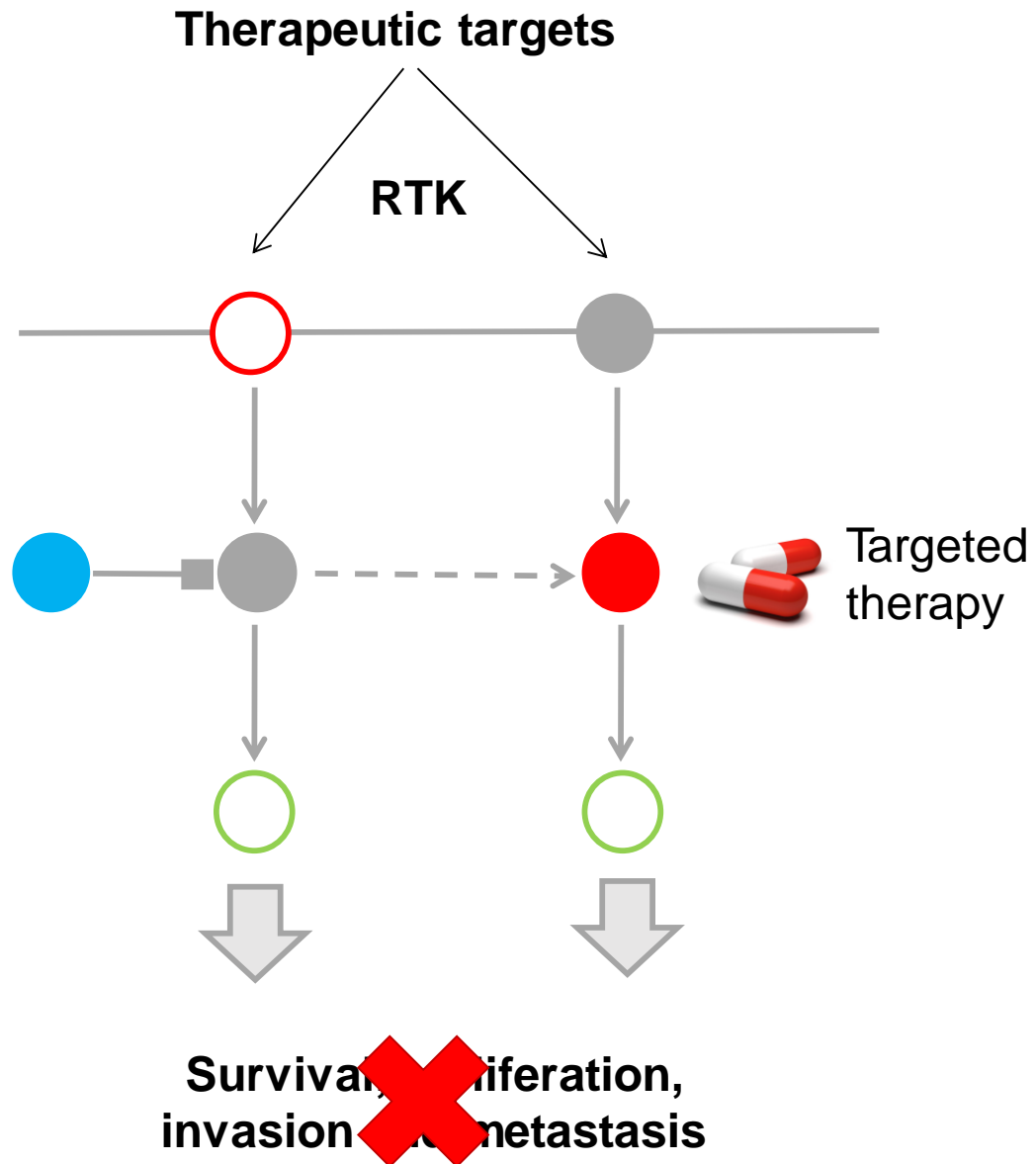
T Altered target gene

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

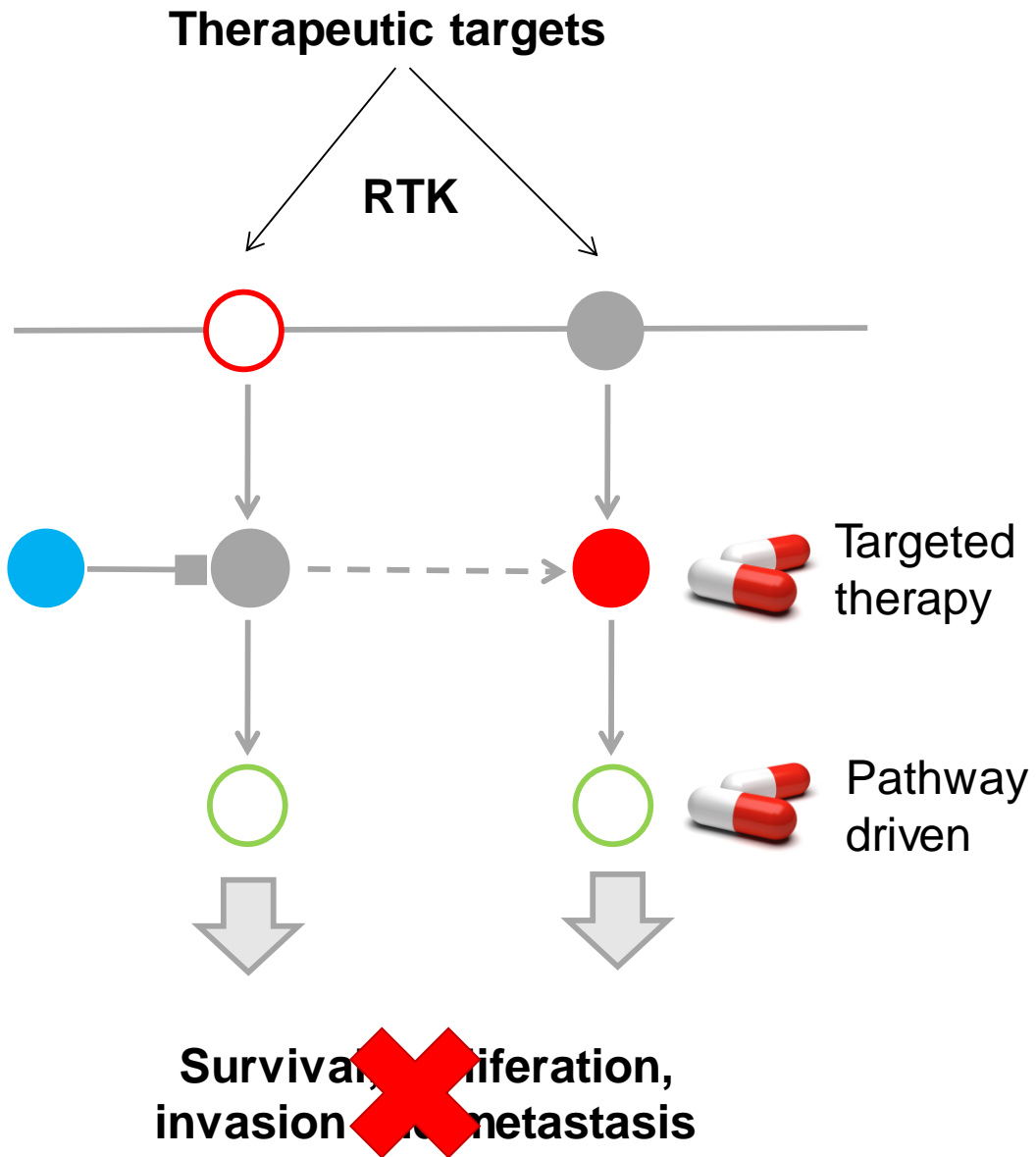


Oncogene mutated



Druggable

1 - Direct pharmacological assignation



Actionable



Wild-type or No Actionable



Tumor suppressor gene mutated



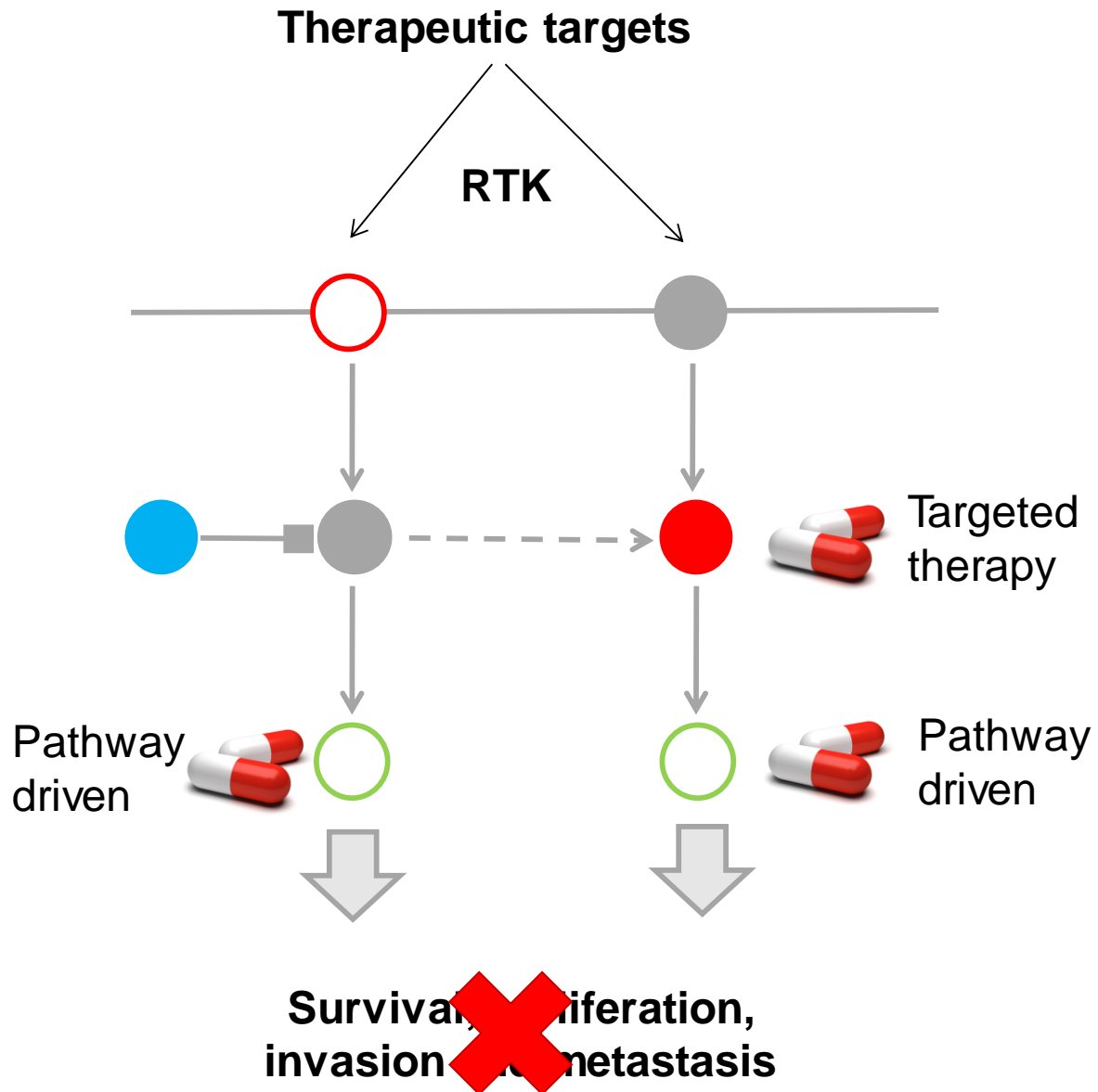
Oncogene mutated



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 assignment

2 - Indirect pharmacological assignment driven by an oncogene

3 - Indirect pharmacological assignment 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

$\text{DScore} = \text{Pre-computed value} - 0.1 + (0.01 * \text{Gene Factor}) + (0.001 * \text{Source Factor})$

Experimental:

$\text{DScore} = \text{Pre-computed value} - 0.0002$ (if **indirect**)

INDIRECT assignments 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 assignment is updated as RESISTANCE and the score turn into negative.

Gene search example



Welcome to PANDRUGS

A resource to study drug-gene interactions in a cancer disease context



Query database! ✓

What is PanDrugs?

PanDrugs database provides a resource for the drug-gene interactions exploration mainly oriented to cancer disease. This database groups relations between compounds and their respective **targets** stored in public databases and **potential biomarkers** identified in cancer cell lines drug response studies.

It also provides extra manual curated information about the drug status and their usage in cancer therapies or clinical studies in this field. All this completed with a ranking score reflecting the strength or evidence level of the association.

The database contains 55880 drug-gene relations of which 51908 are unique, corresponding to 3886 genes and 6048 drugs in different stages.

PanDrugs is supported by the *Spanish National Cancer Research Centre (CNIO)*.

Gene search example

PANDRUGS

Home

Query

About

Query Pandrugs: Genes

Genes

Gene Rank

Enter HUGO Gene symbols

Query

Advanced Options

Drug status level

Cancer

☒ FDA approved ☒ Clinical trials

Other pathologies

☒ FDA approved ☒ Clinical trials ☒ Experimental

Interaction evidence level

☒ Target ☒ Marker

Select Cancer Types

Select all Clear all

Adrenal Gland Bladder Blood Bone Bone Marrow Brain Breast Cancer Cervix Clinical Cancer Colon
Head And Neck Intestine Kidney Liver Lung Neck Nervous System Ovary Pancreas Prostate
Rectum Retina Skin Soft Tissue Stomach Testis Thyroid Uterus

Gene search example

PANDRUGS

Home

Query

About

Query Pandrugs: Genes

Genes

Gene Rank

Select a gene rank file

Browse... No file selected.

Download [sample RNK file](#)

Advanced Options

Drug status level

Cancer

☒ FDA approved ☒ Clinical trials

Other pathologies

☒ FDA approved ☒ Clinical trials ☒ Experimental

Interaction evidence level

☒ Target ☒ Marker

Select Cancer Types

Select all Clear all

Adrenal Gland Bladder Blood Bone Bone Marrow Brain Breast Cancer Cervix Clinical Cancer Colon
Head And Neck Intestine Kidney Liver Lung Neck Nervous System Ovary Pancreas Prostate
Rectum Retina Skin Soft Tissue Stomach Testis Thyroid Uterus

Query

Gene search example

PANDRUGS

Home

Query

About

Query Pandrugs: Genes

Genes [Gene Rank](#)

EGFR
KRAS
TP53

Input genes

Query

All parameters by default

Advanced Options

Drug status level

Cancer

☒ FDA approved ☒ Clinical trials

Other pathologies

☒ FDA approved ☒ Clinical trials ☒ Experimental

Interaction evidence level

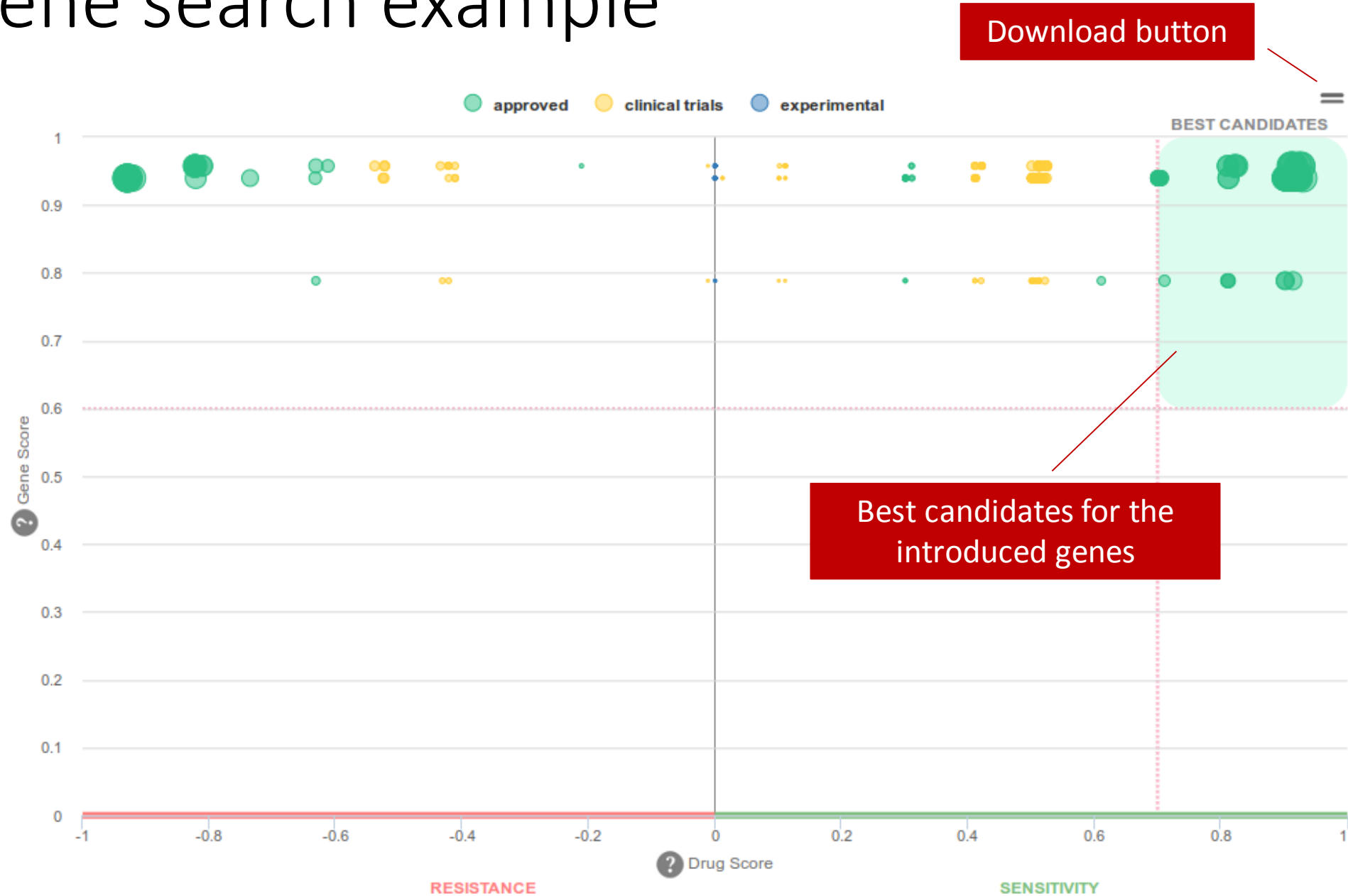
☒ Target ☒ Marker

Select Cancer Types

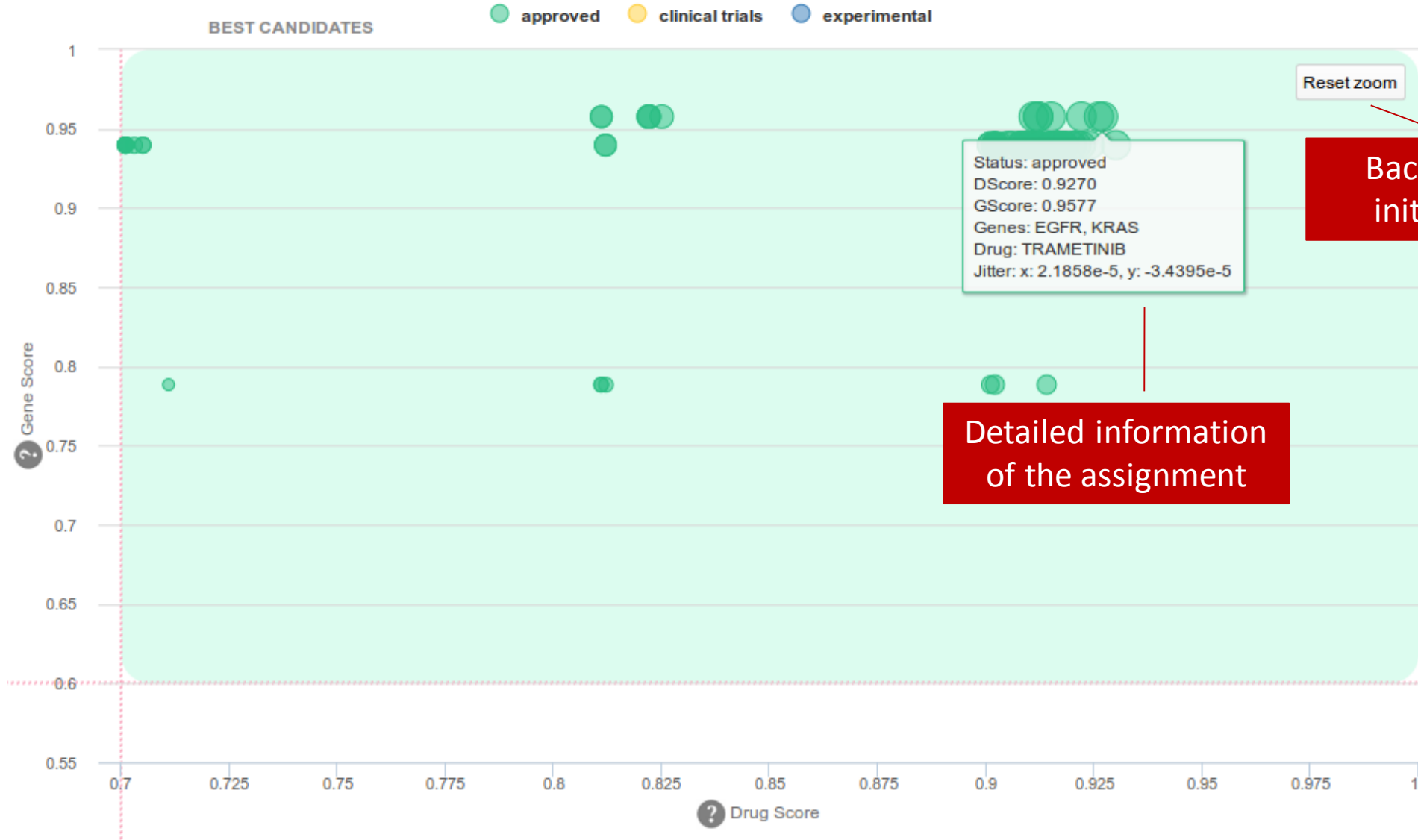
Select all Clear all

Adrenal Gland Bladder Blood Bone Bone Marrow Brain Breast Cancer Cervix Clinical Cancer Colon
Head And Neck Intestine Kidney Liver Lung Neck Nervous System Ovary Pancreas Prostate
Rectum Retina Skin Soft Tissue Stomach Testis Thyroid Uterus

Gene search example

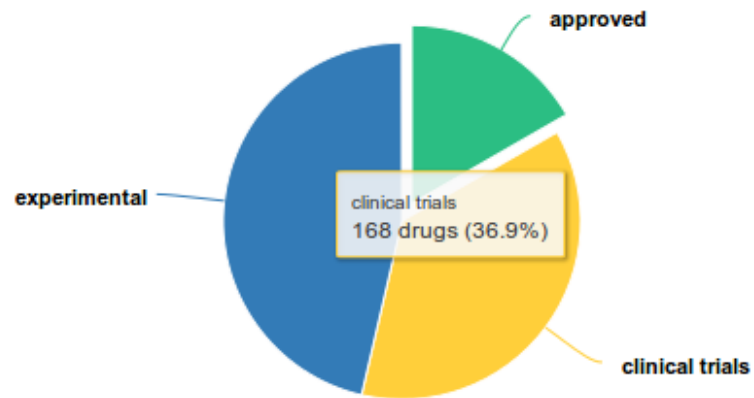


Gene search example

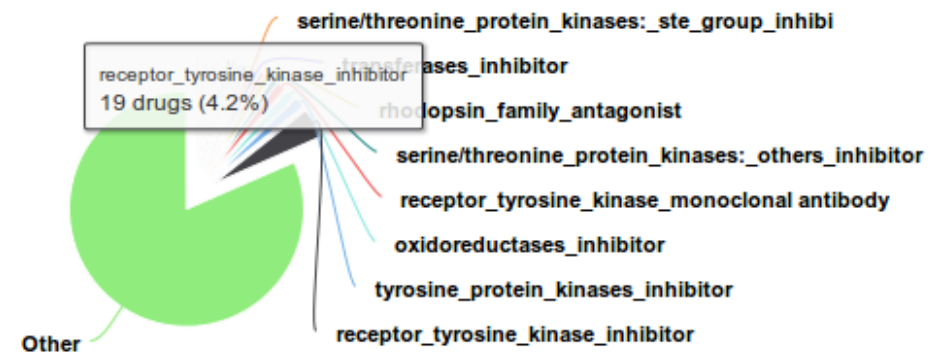


Gene search example

Drugs by approval status



Drugs by family



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 GiPI MCG PGKB TALC TCGA TEND TTD TCT moAb	Approved for colon and rectum cancer	Targeted therapy		0.9300	0.9577
	KRAS and EGFR	TRAMETINIB	serine/threonine_protein_kinases:_ste_group_inhibi	CC CFB DB GiPI MCG MCGCT TALC TCT	Approved for skin cancer	Targeted therapy		0.9270	0.9577
	KRAS and EGFR	COBIMETINIB	Other	CC CFB DB MCG MCGCT TALC TCT	Approved for skin cancer	Targeted therapy		0.9260	0.9577
	KRAS and EGFR	REGORAFENIB	receptor_tyrosine_kinase_inhibitor	DB GiPI MCG MCGCT	Approved for colon, intestine, rectum and stomach cancer	Targeted therapy		0.9240	0.9577
	EGFR	LAPATINIB	receptor_tyrosine_kinase_inhibitor	CIV CC CFB CFCT DoCM DB GDSC GiPI MCG PGKB TALC TCGA TEND TTD TCT	Approved for breast cancer	Targeted therapy		0.9200	0.9398
	EGFR	TRASTUZUMAB	receptor_tyrosine_kinase_monoclonal antibody	CIV CFB CFCT DoCM DB GiPI MCG PGKB TALC TCGA TEND TTD TCT moAb	Approved for breast and stomach cancer	Targeted therapy		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		0.9180	0.9577
	EGFR	PERTUZUMAB	receptor_tyrosine_kinase_monoclonal antibody	CFB DB GiPI MCG PGKB TALC TCGA TTD TCT moAb	Approved for breast cancer	Targeted therapy		0.9180	0.9398
	EGFR	AFATINIB	receptor_tyrosine_kinase_inhibitor	CC DB GDSC GiPI MCG MCGCT TALC TTD TCT	Approved for lung cancer	Targeted therapy		0.9170	0.9398

	KRAS and EGFR	TRAMETINIB	serine/threonine_protein_kinases:_ste_group_inhibi	CC CFB DB GiPI MCG MCGCT TALC TCT	Approved for skin cancer	Targeted therapy		0.9270	0.9577
TRAMETINIB is a drug approved by FDA that acts as an inhibitor of MAP2K1, a protein downstream of 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				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	ClarityFoundationBiomarkers				0.8220	0.9577

THE END

Fátima Al-Shahrour
falshahrour@cnio.es

Javier Perales-Patón
jperales@cnio.es

Elena Piñeiro-Yáñez
epineiro@cnio.es