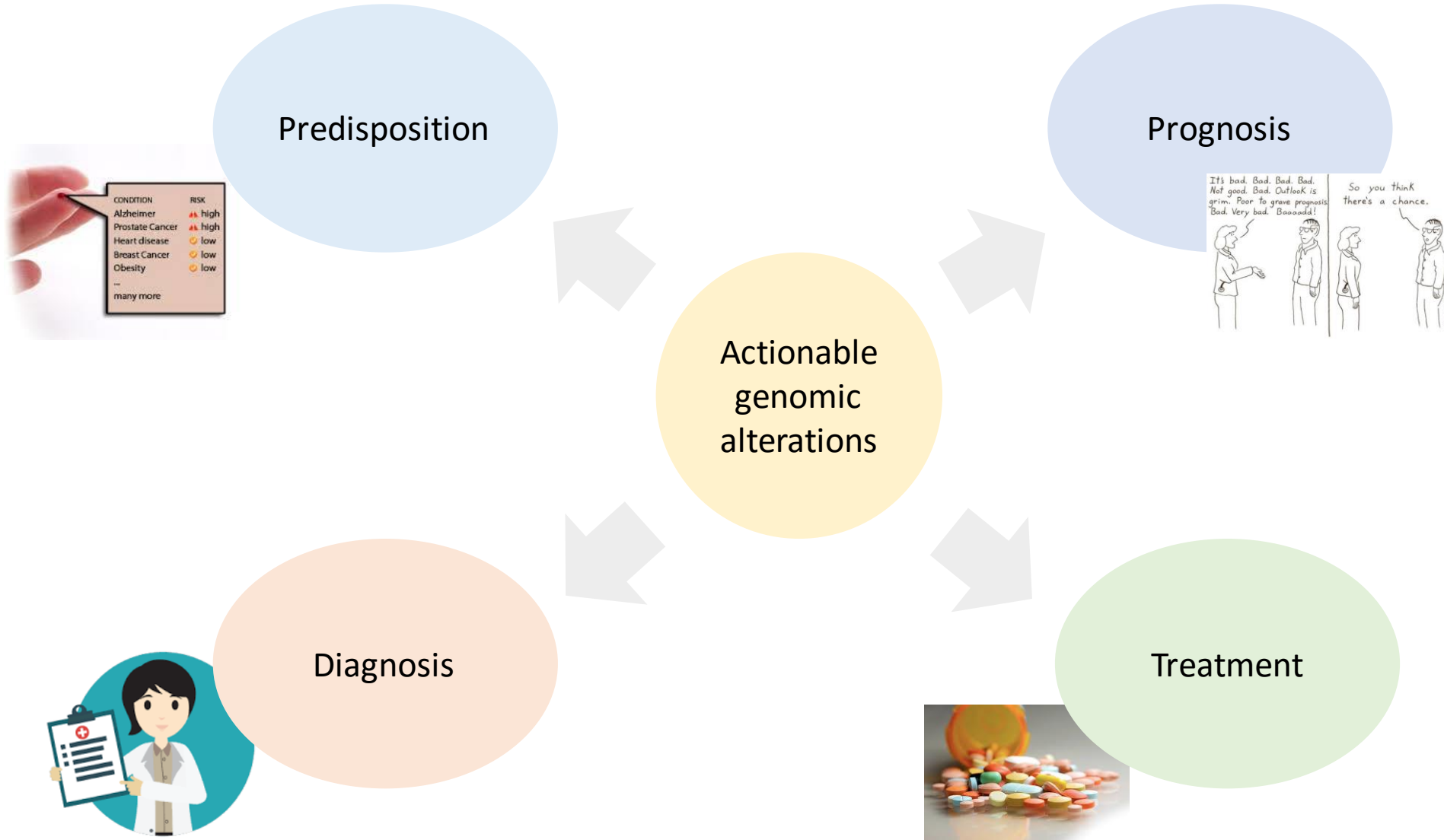


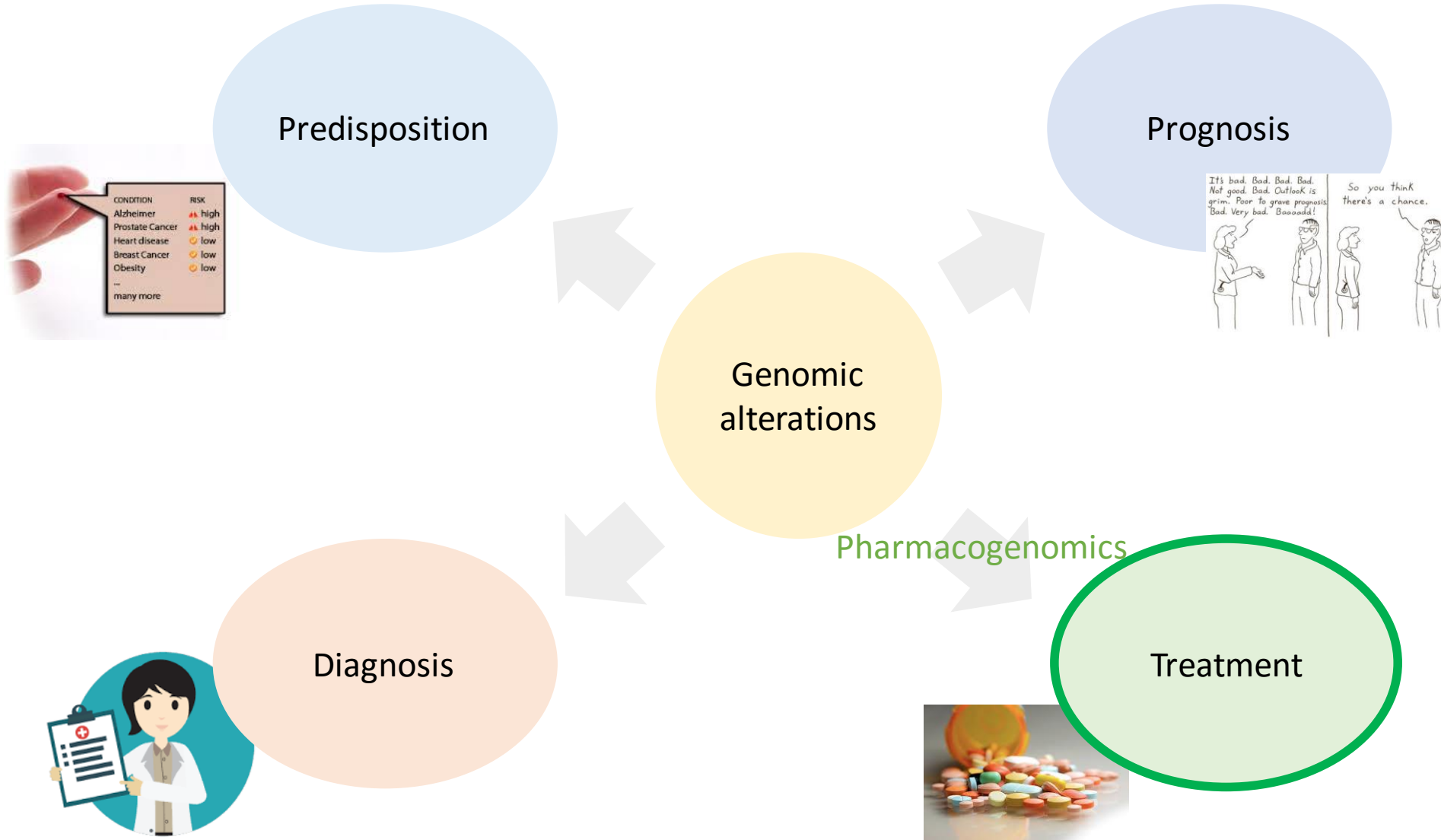
# Precision medicine: NGS variant analysis and interpretation for translational research

PanDrugs: Matching mutations with therapies

Fátima Al-Shahrour ● Javier Perales ● Elena Piñeiro

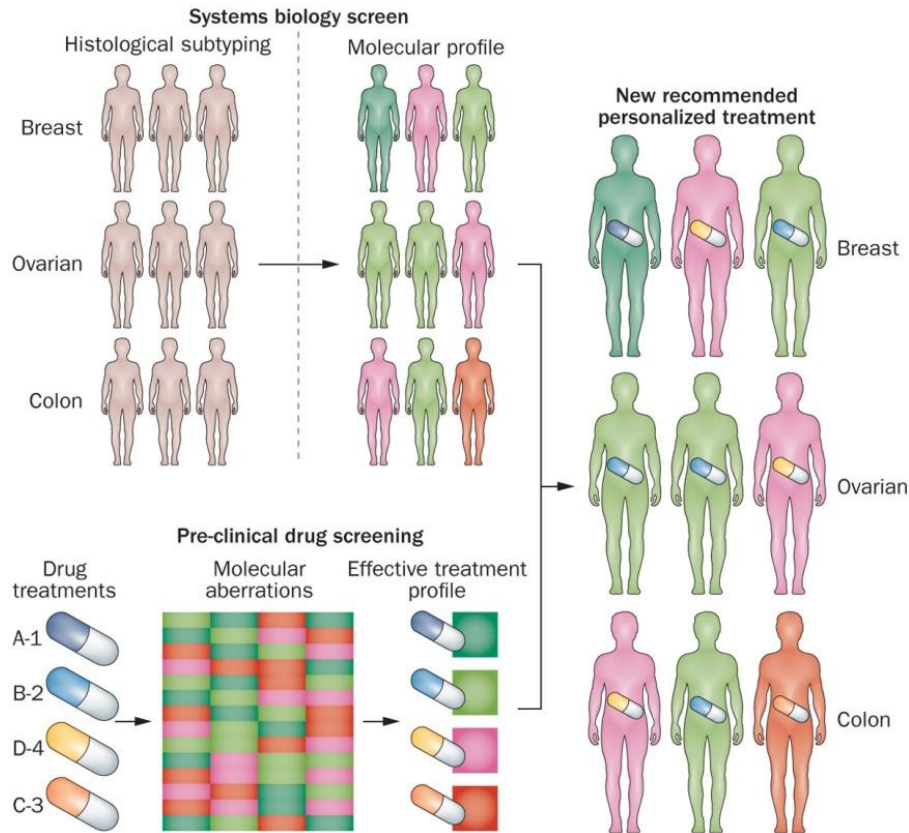
September 16, 2017





# Pharmacogenomics

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



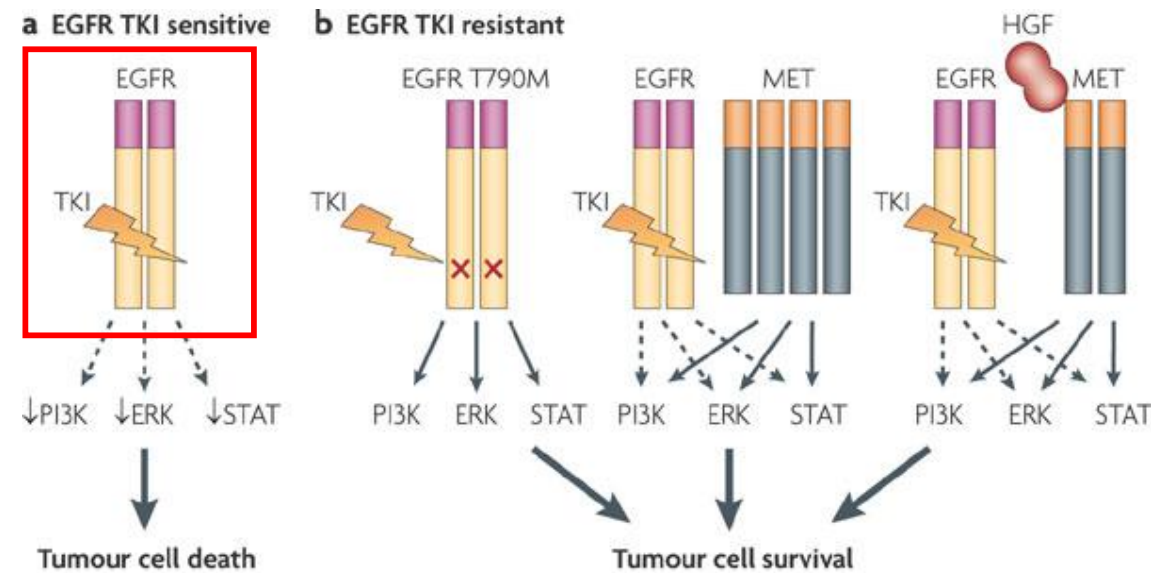
- Breaks the rule "one size fits all"
- Individual variation predicts:
  - Response
  - No response
  - Side effects
- Tailors a suitable treatment for a stratified patient

# Gene-drug considerations

- Target/Biomarker

# Target & marker genes

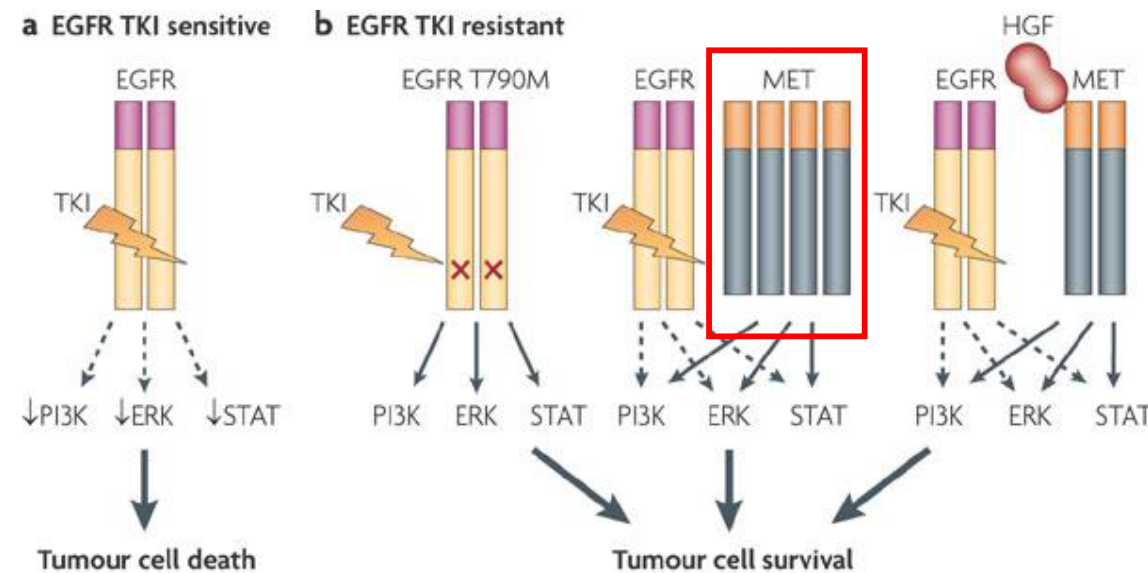
**TARGET** human gene that **contributes to a disease phenotype** and can be targeted directly by a drug (small molecule, monoclonal antibody, ...)



# 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

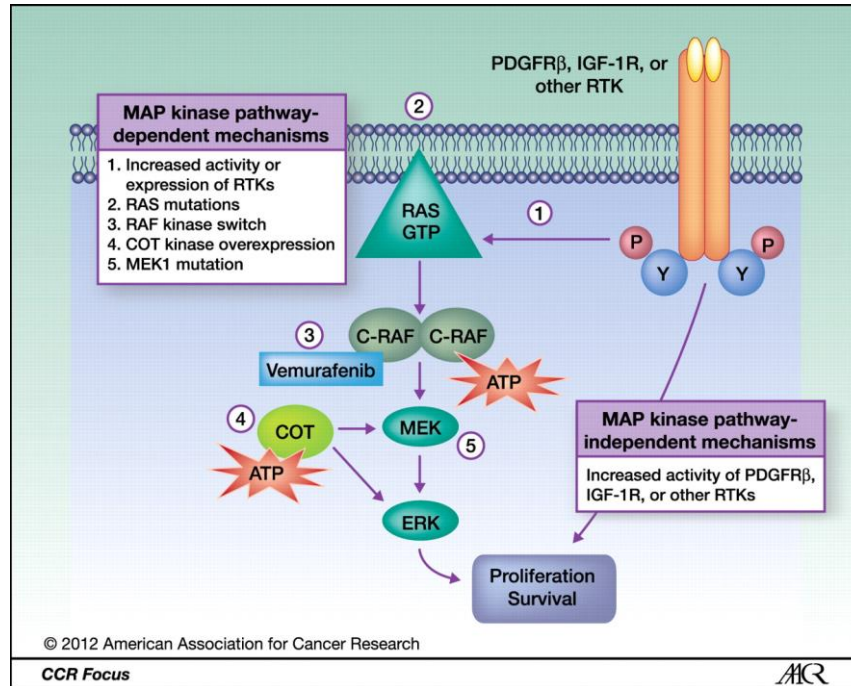


# Gene-drug considerations

- Target/Biomarker
- Sensitivity/Resistance



# Sensitivity vs Resistance

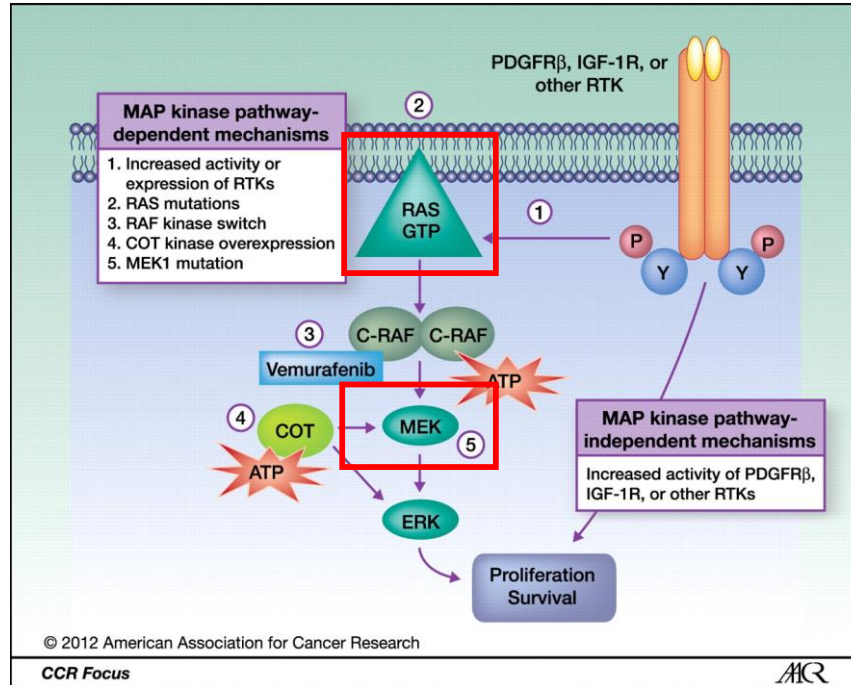


**Advanced or metastatic pancreatic cancer**

**Melanoma treatment with BRAF mutation**

**VEMURAFENIB**

# Sensitivity vs Resistance



Melanoma treatment with BRAF mutation

VEMURAFENIB



Advanced or metastatic pancreatic cancer

APC ★

FBXW7 ★

# 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

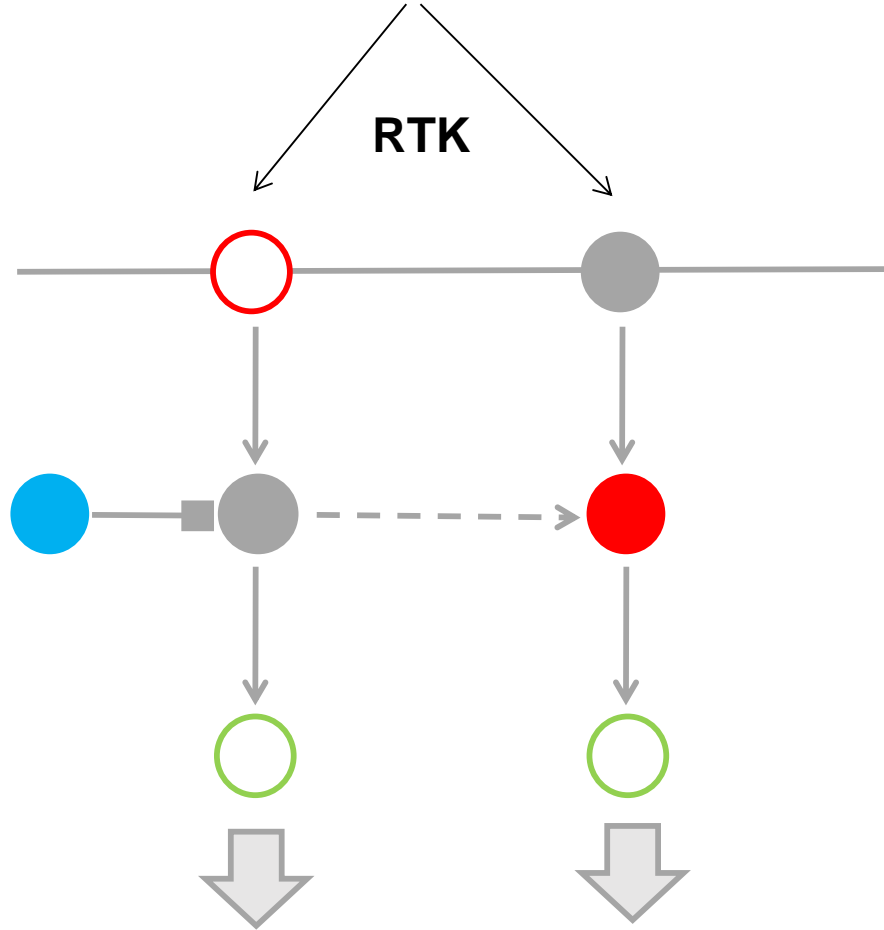
**T** Altered target gene

**G** Altered non target gene

**T** Wild type target gene

## Therapeutic targets

RTK



Actionable



Wild-type or No Actionable



Tumor suppressor gene mutated

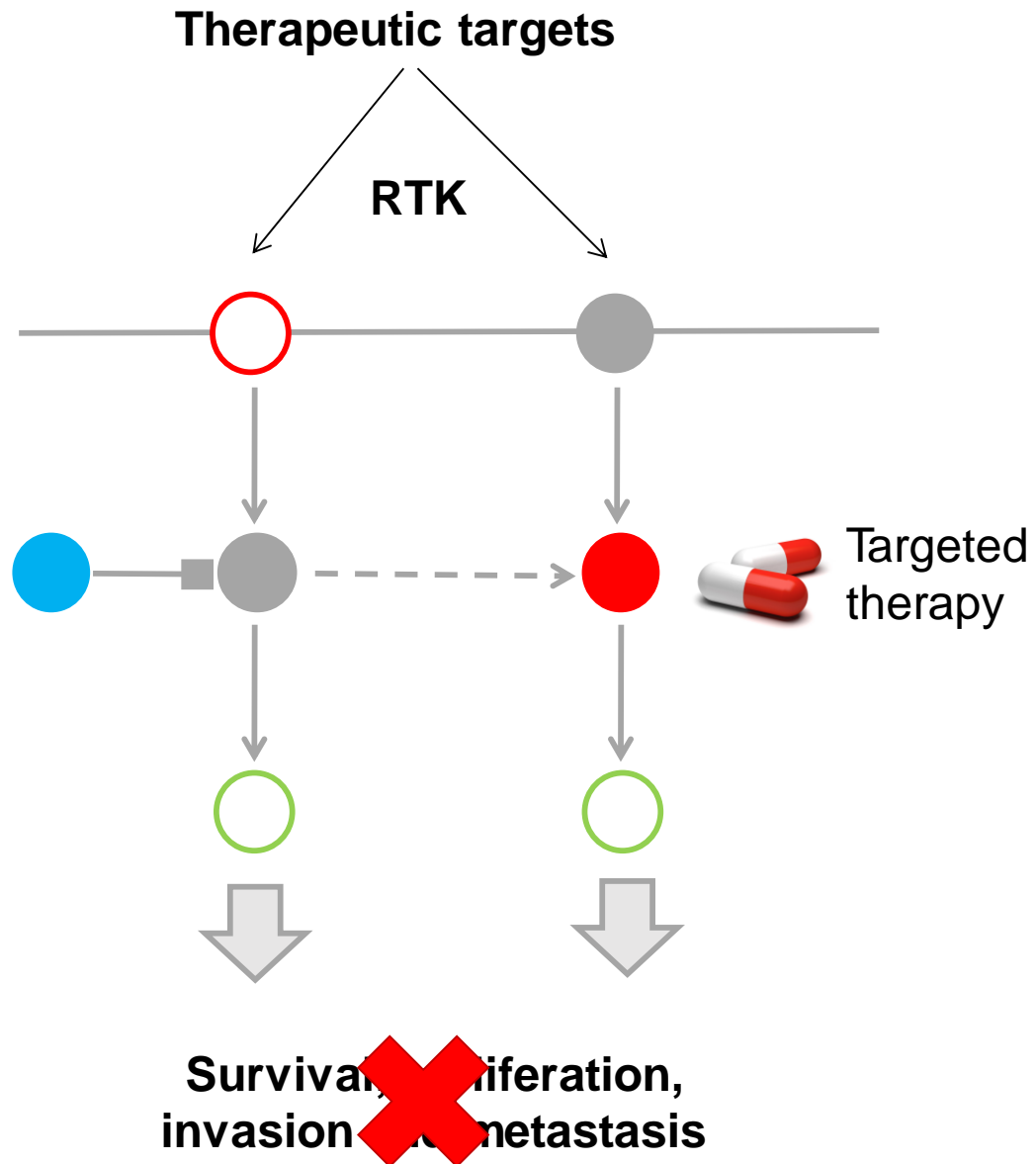


Oncogene mutated



Druggable

**Survival, proliferation,  
invasion and metastasis**



Actionable



Wild-type or No Actionable



Tumor suppressor gene mutated

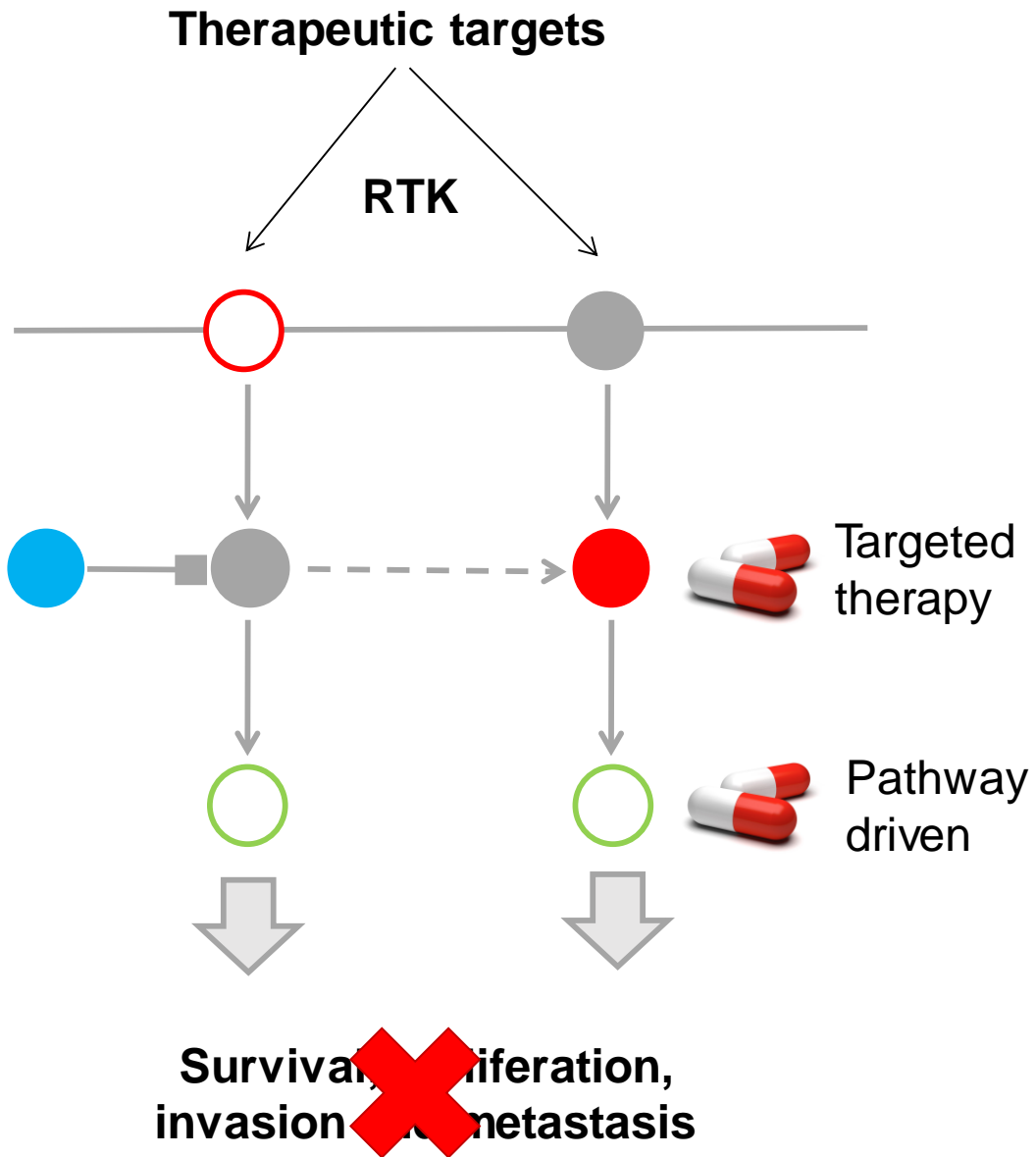


Oncogene mutated



Druggable

1 - Direct pharmacological assignation



Actionable



Wild-type or No Actionable



Tumor suppressor gene mutated



Oncogene mutated

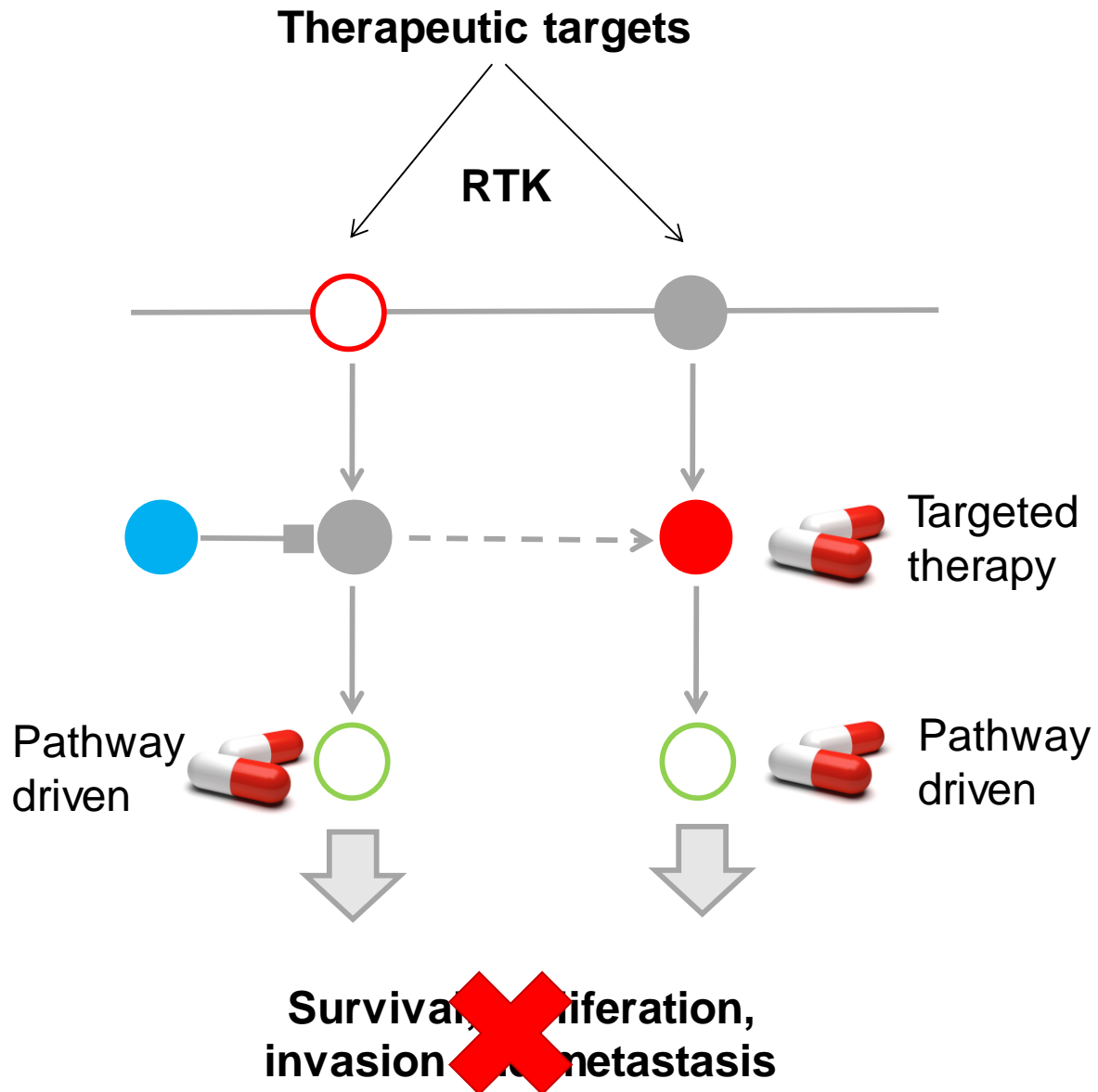


Druggable

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 considerations

- Approval Status

# Approval status

## Approved

Same condition

Other



Repurposing



## Clinical trials

Same condition clinical trials

Other



Repurposing

*ClinicalTrials.gov*

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



## Experimental

## Withdrawn

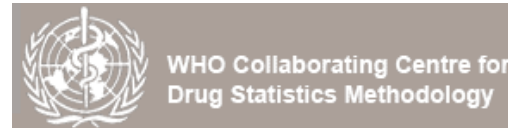
# Drug considerations

- Approval Status
- Classifications

Target-based classification of drugs



Anatomical Therapeutic Chemical (ATC) classification of drugs



Mechanism of Action (MOA) classification of drugs

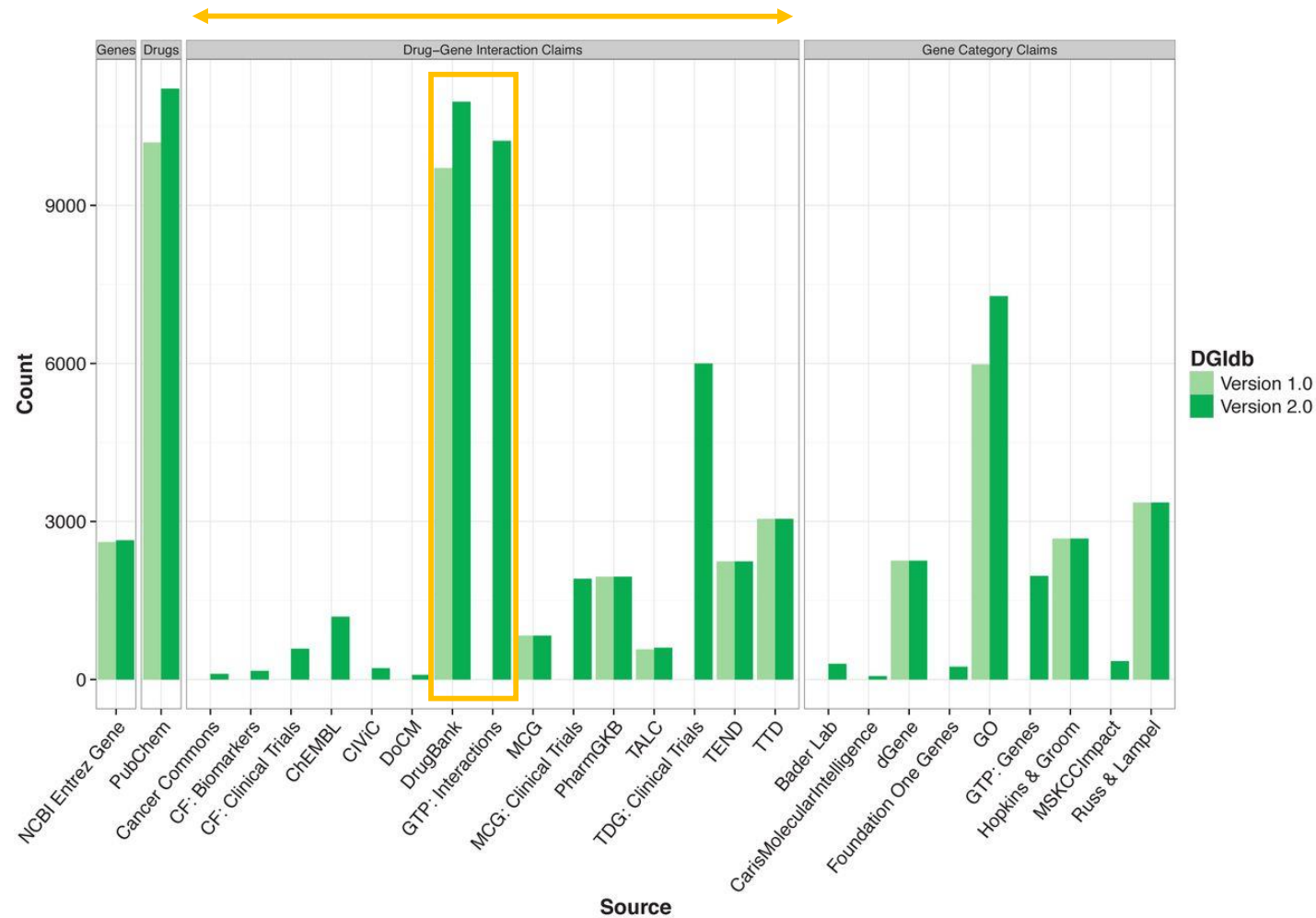


# Drug considerations

- 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  
**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

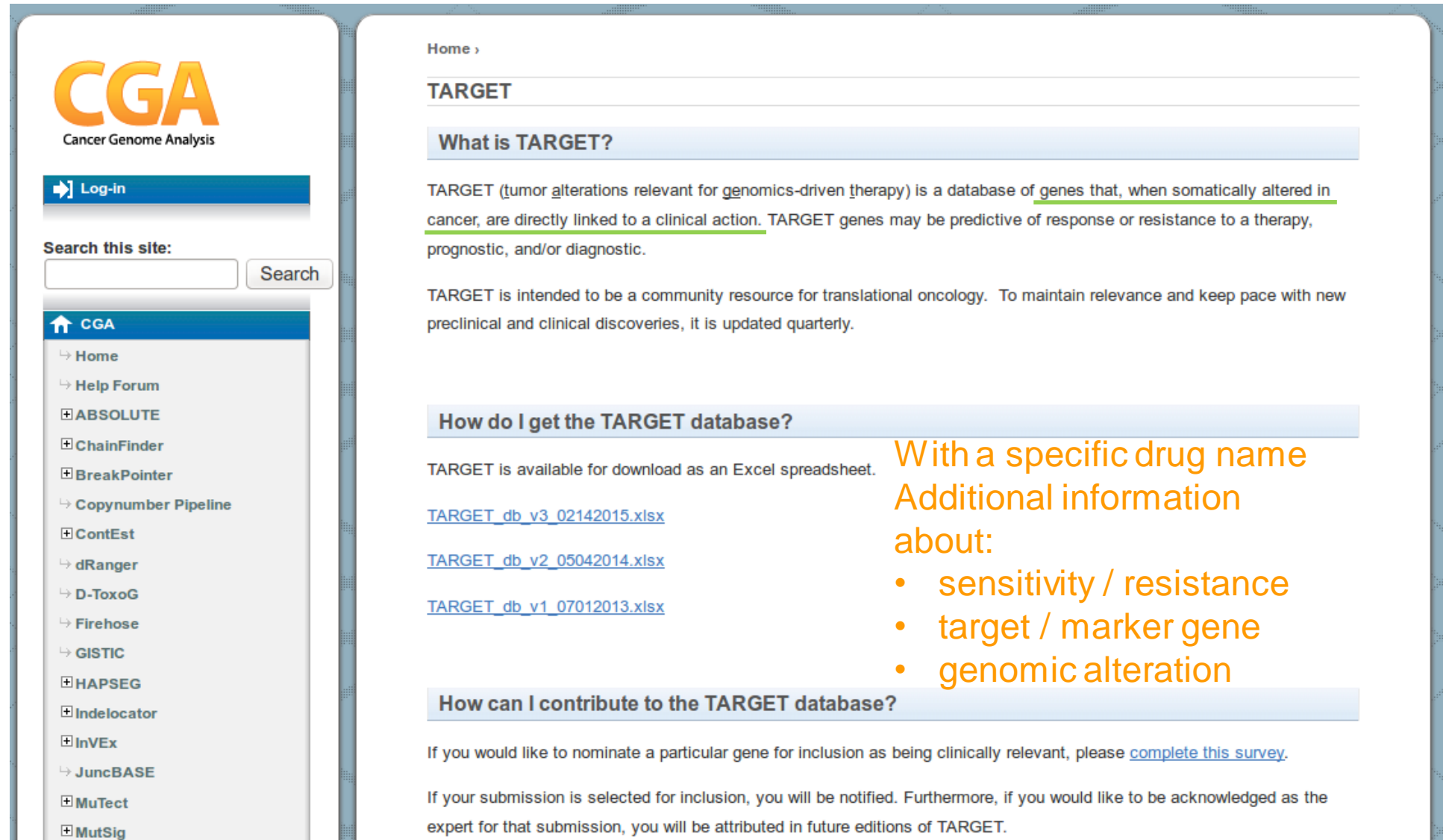
**PharmGKB:** with potentially clinically actionable drug-gene associations

**TALC:** targeted agents in lung cancer

**TEND:** manual curation of FDA approved drugs and their targets from DrugBank

**TTD:** therapeutic targets and corresponding drugs

# Drug-gene association resources: TARGET



The screenshot shows the CGA (Cancer Genome Analysis) website. The left sidebar contains the CGA logo and a list of navigation links: Home, Help Forum, ABSOLUTE, ChainFinder, BreakPointer, Copynumber Pipeline, ContEst, dRanger, D-ToxoG, Firehose, GISTIC, HAPSEG, Indelocator, InVEx, JuncBASE, MuTect, and MutSig. The main content area is titled 'TARGET' and includes a 'What is TARGET?' section, a 'How do I get the TARGET database?' section, and a 'How can I contribute to the TARGET database?' section.

**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.

# 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)

[https://en.wikipedia.org/wiki/List\\_of\\_therapeutic\\_monoclonal\\_antibodies](https://en.wikipedia.org/wiki/List_of_therapeutic_monoclonal_antibodies)

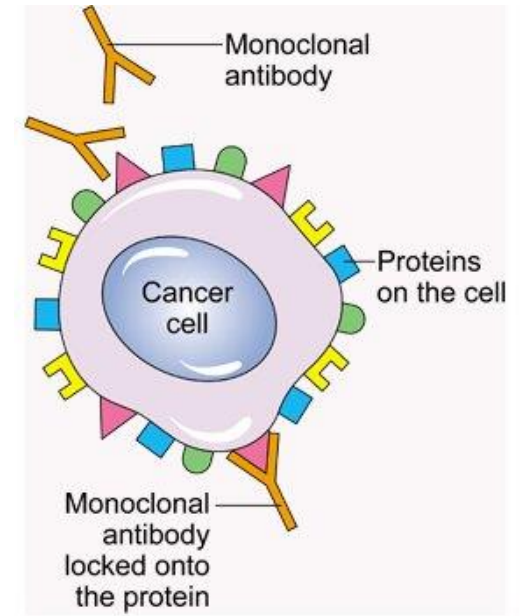


Diagram showing a monoclonal antibody attached to a cancer cell  
© CancerHelp UK

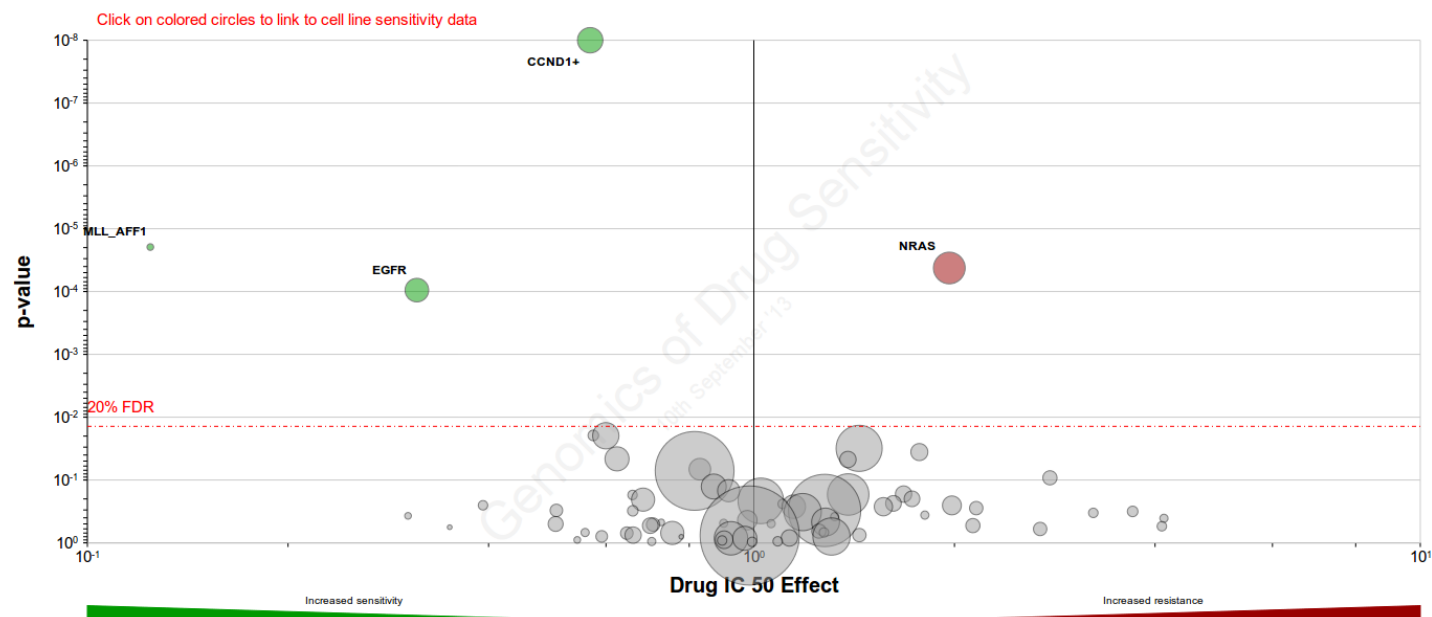
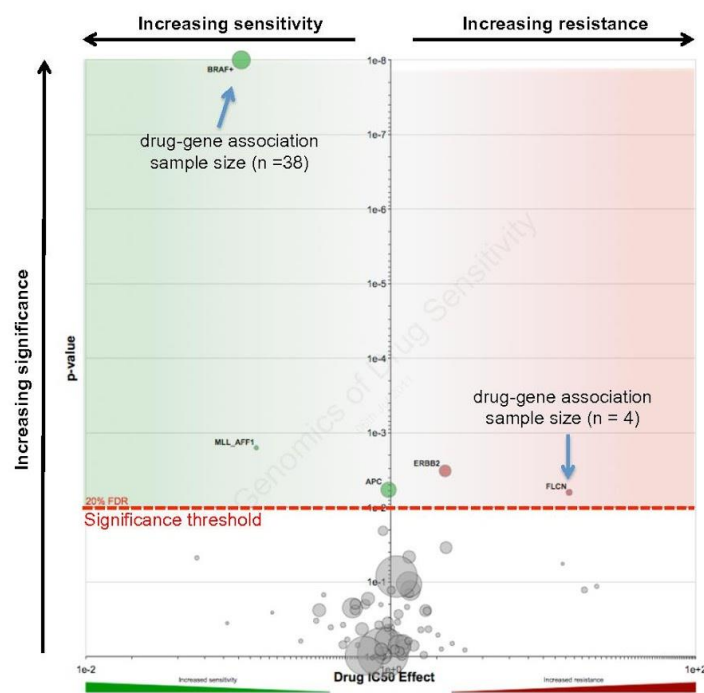


# Drug-gene association resources: GDSC

<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



Search all columns:

Show 10 entries

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

# 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.

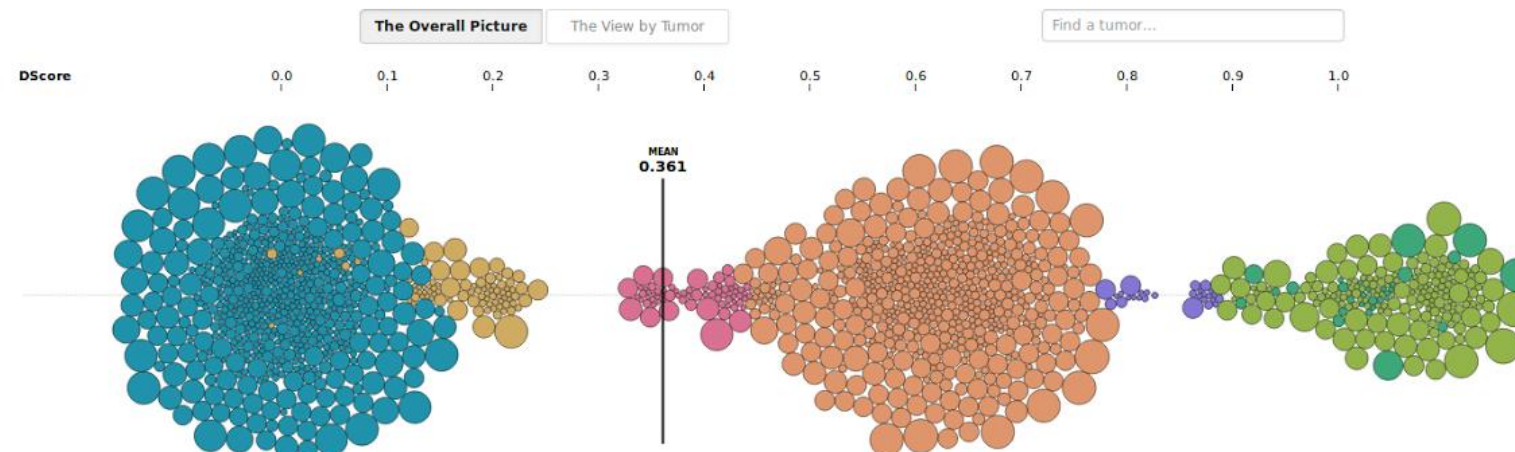
Using 4 alternative inputs (e.g. standard VCF files, RNK files, gene list and drug query), **PanDrugs** identify actionable molecular alterations and prioritize drugs by calculating gene-drug scores which takes into account: i) genomic feature evidence by mutation impact score; ii) target pathway context; 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

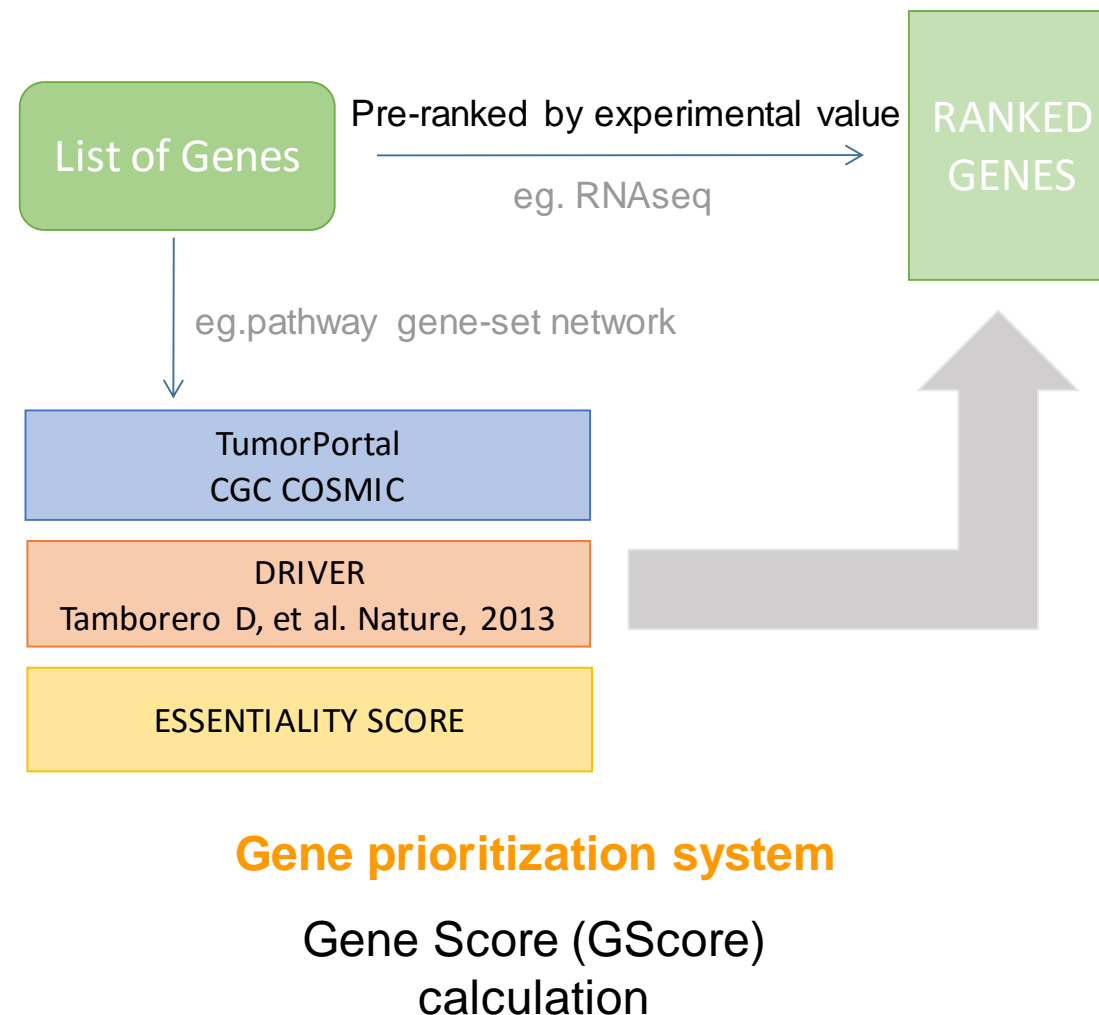
## Query PanDrugs

Genes Drugs Gene Ranking Genomic Variants

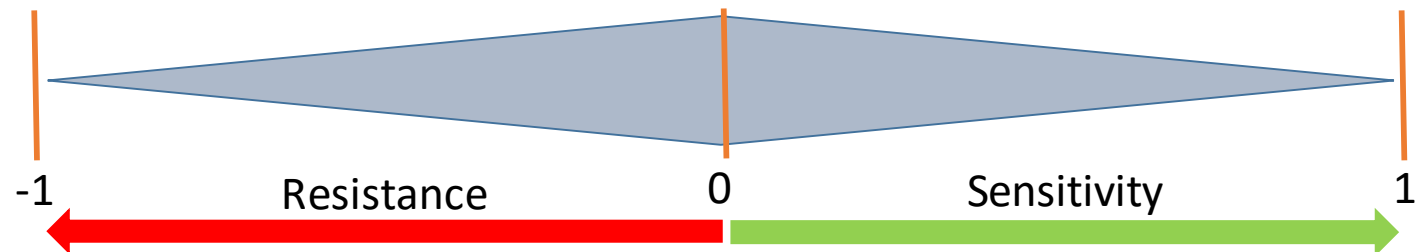
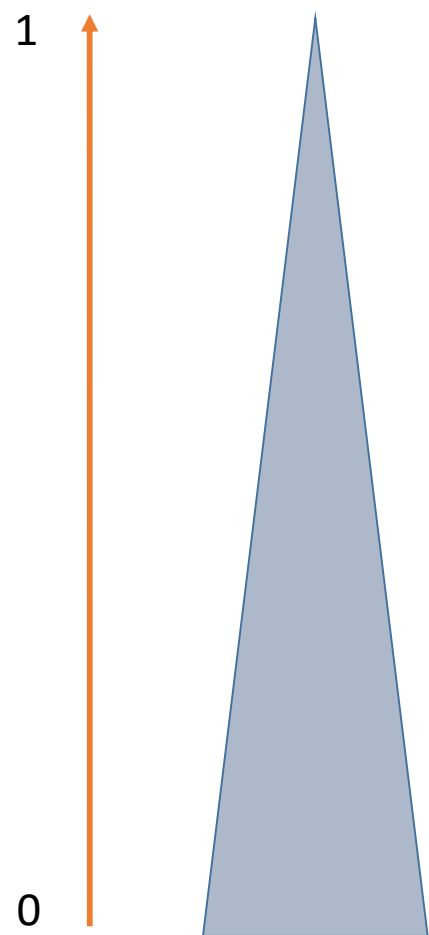
Provide a gene list (HUGO Gene Symbols) to retrieve PanDrugs therapeutic candidates. Supply one gene symbol per each line.

Use an example

Query



# 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)

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

## 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

PANDRUGS

Home Query Login Help API

Welcome to

# PANDRUGS

A novel method for prioritizing therapies using individual genomic data

Query! ✓

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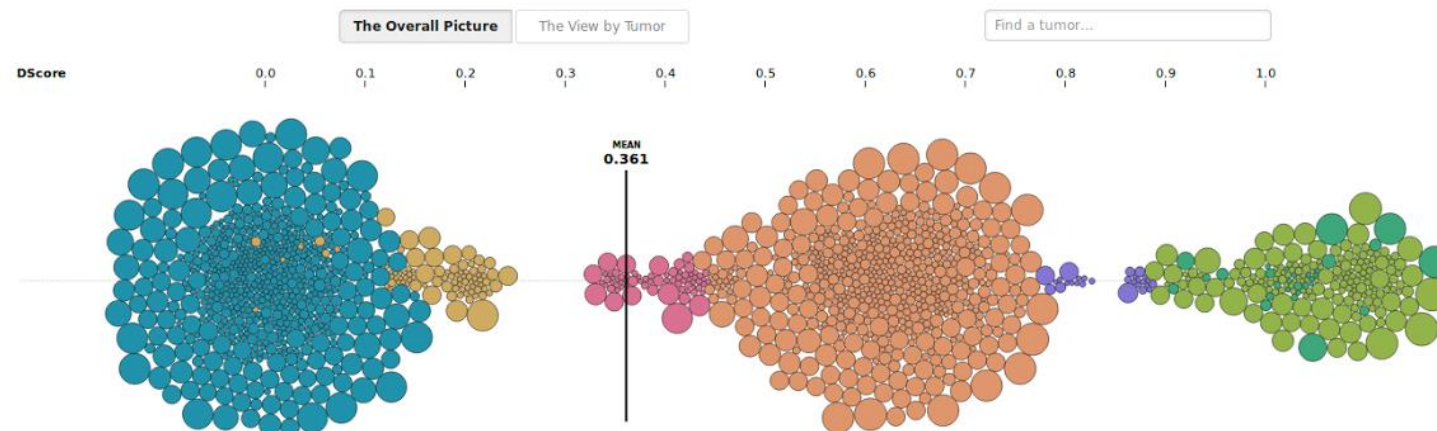
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# Gene search example

**PANDRUGS** [Home](#) [Query](#) [Login](#) [Help](#) [API](#)

## Query PanDrugs

[Genes](#) [Drugs](#) [Gene Ranking](#) [Genomic Variants](#)

[Use an example](#)

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

Login

Help

API

## Query PanDrugs

Genes

Drugs

Gene Ranking

Genomic Variants

Select a gene ranking file

Browse ...

[Download a ranked list example](#) (Lung adenocarcinoma LUAD patient with EGFR mutation and amplification from TCGA)

### 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

Login

Help

API

Query PanDrugs

Genes

Drugs

Gene Ranking

Genomic Variants

Use an example

EGFR  
KRAS  
TP53

Input genes

Query

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

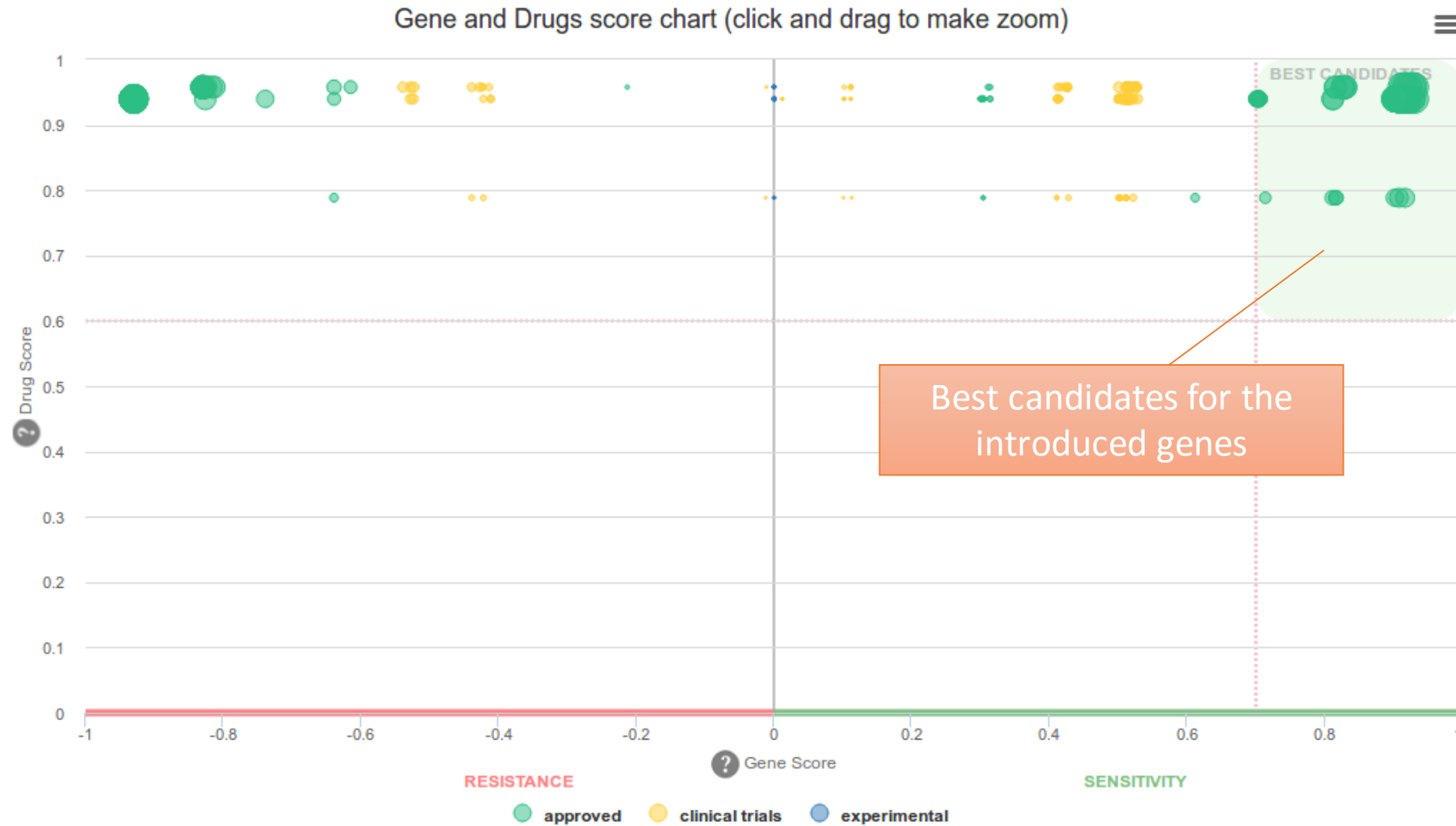
Select Cancer Types

Select allClear all

Adrenal GlandBladderBloodBoneBone MarrowBrainBreastCancerCervixClinical CancerColonHead And NeckIntestineKidneyLiverLungNeckNervous SystemOvaryPancreasProstateRectumRetinaSkinSoft TissueStomachTestisThyroidUterus

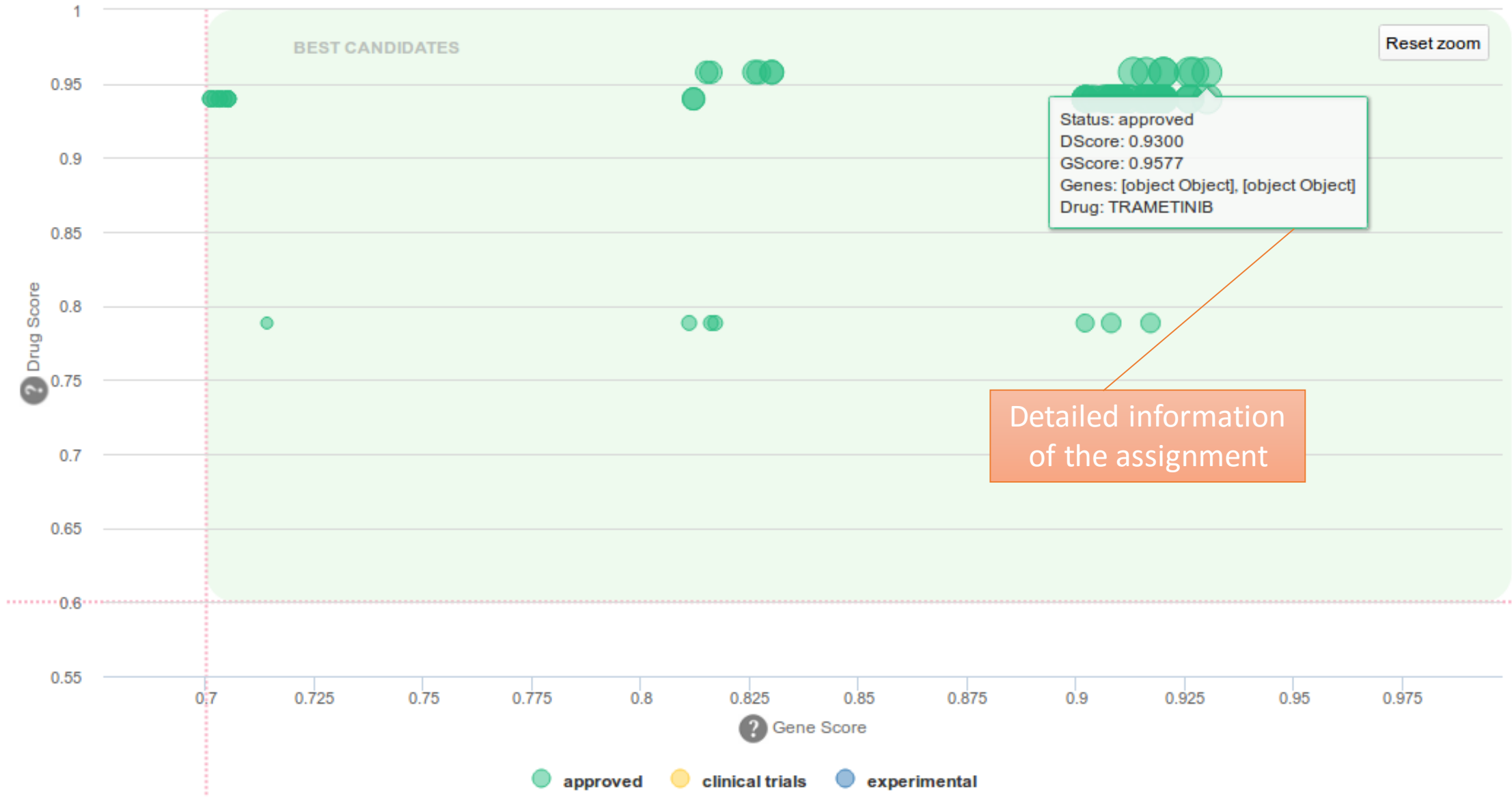
A collaboration between [Traslational Bioinformatics Unit \(CNIO\)](#) & [SING \(U. Vigo\)](#)

# Gene search example



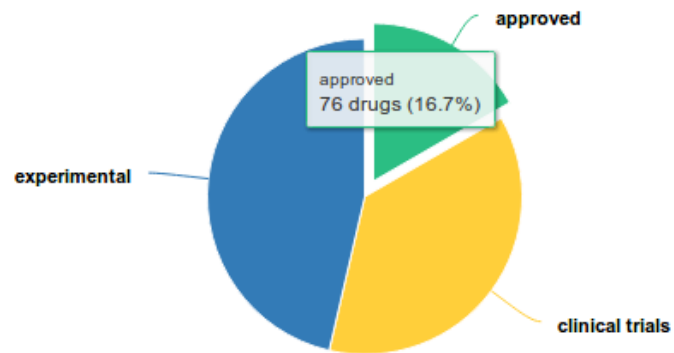
# Gene search example

Gene and Drugs score chart (click and drag to make zoom)

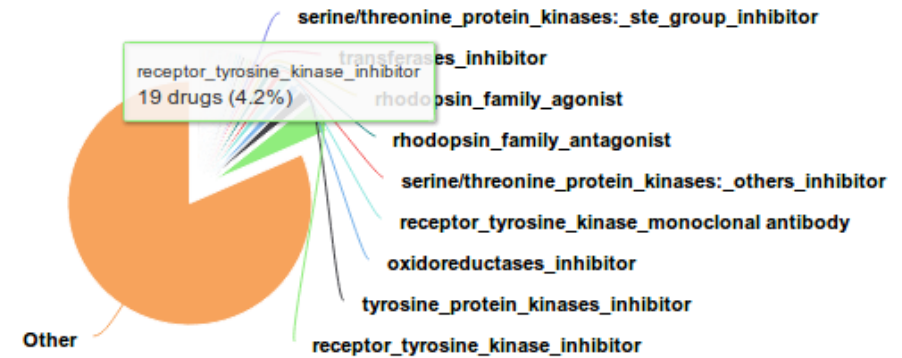


# Gene search example

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 ?
<div>+</div>	EGFR and KRAS	TRAMETINIB	serine/threonine_protein_kinases:_ste_group_inhibitor	<div>CIVCCCFBDoCMBDBGiPIMCGMCGCTTALCTCT</div>	Approved for skin cancer	Targeted therapy	<div><div>G</div>→<div>T</div><div>T</div><div>D</div></div>	0.9300	0.9577
<div>+</div>	EGFR and KRAS	CETUXIMAB	receptor_tyrosine_kinase_monoclonal_antibody	<div>CIVCCCFBDoCMBDBGiPIMCGPGKBTALCTCGATENDTTDTCTmoAb</div>	Approved for colon and rectum cancer	Targeted therapy	<div><div>T</div><div>T</div><div>D</div></div>	0.9300	0.9577
<div>+</div>	EGFR and KRAS	COBIMETINIB	Other	<div>CCCFBDBMCGMCGCTTALCTCT</div>	Approved for skin cancer	Targeted therapy	<div><div>G</div>→<div>T</div><div>T</div><div>D</div></div>	0.9270	0.9577
<div>+</div>	EGFR and KRAS	REGORAFENIB	receptor_tyrosine_kinase_inhibitor	<div>DBGiPIMCGMCGCTTALCTCT</div>	Approved for colon, intestine, rectum and stomach cancer	Targeted therapy	<div><div>G</div>→<div>T</div><div>T</div><div>D</div></div>	0.9260	0.9577
<div>+</div>	EGFR	TRASTUZUMAB	receptor_tyrosine_kinase_monoclonal_antibody	<div>CIVCFB CFCTDoCMBDBGiPIMCGPGKBTALCTCGATENDTTDTCTmoAb</div>	Approved for breast and stomach cancer	Targeted therapy	<div><div>T</div><div>T</div><div>D</div></div>	0.9200	0.9398
<div>+</div>	EGFR	LAPATINIB	receptor_tyrosine_kinase_inhibitor	<div>CIVCCCFB CFCTDoCMBDBGDSCGiPIMCGPGKBTALCTCGATENDTTDTCT</div>	Approved for breast cancer	Targeted therapy	<div><div>T</div><div>T</div><div>D</div></div>	0.9200	0.9398
<div>+</div>	EGFR and KRAS	SORAFENIB	receptor_tyrosine_kinase_inhibitor	<div>CIVCFCTDoCMBDBGDSCGiPIMCGMCGCTPGKBTALCTCGATENDTTDTCT</div>	Approved for kidney cancer	Targeted therapy	<div><div>G</div>→<div>T</div><div>T</div><div>D</div></div>	0.9200	0.9577
<div>+</div>	EGFR	PERTUZUMAB	receptor_tyrosine_kinase_monoclonal_antibody	<div>CFBDoCMBDBGiPIMCGPGKBTALCTCGATTDCTmoAb</div>	Approved for breast cancer	Targeted therapy	<div><div>T</div><div>T</div><div>D</div></div>	0.9190	0.9398
<div>+</div>	TP53	PACLITAXEL	rhodopsin_family_antagonist	<div>CIVCFB CFCTDBGDSCGiPIMCGPGKBTENDTTDTCT</div>	Approved for breast, lung, ovary and pancreas cancer	Chemotherapy	<div><div>G</div>→<div>T</div><div>T</div><div>D</div></div>	0.9170	0.7884
<div>+</div>	EGFR	AFATINIB	receptor_tyrosine_kinase_inhibitor	<div>CCDBGDSCGiPIMCGMCGCTTALCTTDCT</div>	Approved for lung cancer	Targeted therapy	<div><div>T</div><div>T</div><div>D</div></div>	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	<a href="#">CIV</a> <a href="#">CC</a> <a href="#">CFB</a> <a href="#">DoCM</a> <a href="#">DB</a> <a href="#">GtPI</a> <a href="#">MCG</a> <a href="#">MCGCT</a> <a href="#">TALC</a> <a href="#">TCT</a>	Approved for skin cancer	Targeted therapy		0.9300	0.9577
	<p>TRAMETINIB is a drug approved by FDA that acts as an inhibitor of MAP2K1, a protein downstream to EGFR and KRAS</p> <p><b>EGFR and KRAS</b></p> <p>Sensitivity: SENSITIVITY / RESISTANCE</p> <p>Alteration: WT (sensitivity) / Missense_mutation (resistance)</p> <p>Find more info for "TRAMETINIB"+"MAP2K1" in: <a href="#">[PubMed]</a> <a href="#">[ClinicalTrials.gov]</a></p>		serine/threonine_protein_kinases:_ste_group_inhibitor	CIVIC, CancerCommons, ClearityFoundationBiomarkers, DoCM, DrugBank, GuideToPharmacologyInteractions, MyCancerGenome, MyCancerGenomeClinicalTrial, TALC, TdgClinicalTrial			<div>See pathways</div>	0.9300	0.9577
	<p>Molecular alterations in KRAS are associated with response to TRAMETINIB, a drug approved by FDA</p> <p><b>KRAS</b></p> <p>Sensitivity: SENSITIVITY</p> <p>Alteration: Missense_mutation</p> <p>Find more info for "TRAMETINIB"+"KRAS" in: <a href="#">[PubMed]</a> <a href="#">[ClinicalTrials.gov]</a></p>		serine/threonine_protein_kinases:_ste_group_inhibitor	CIVIC, CancerCommons, ClearityFoundationBiomarkers, DoCM, DrugBank, GuideToPharmacologyInteractions, MyCancerGenome, MyCancerGenomeClinicalTrial, TALC, TdgClinicalTrial				0.8300	0.9577