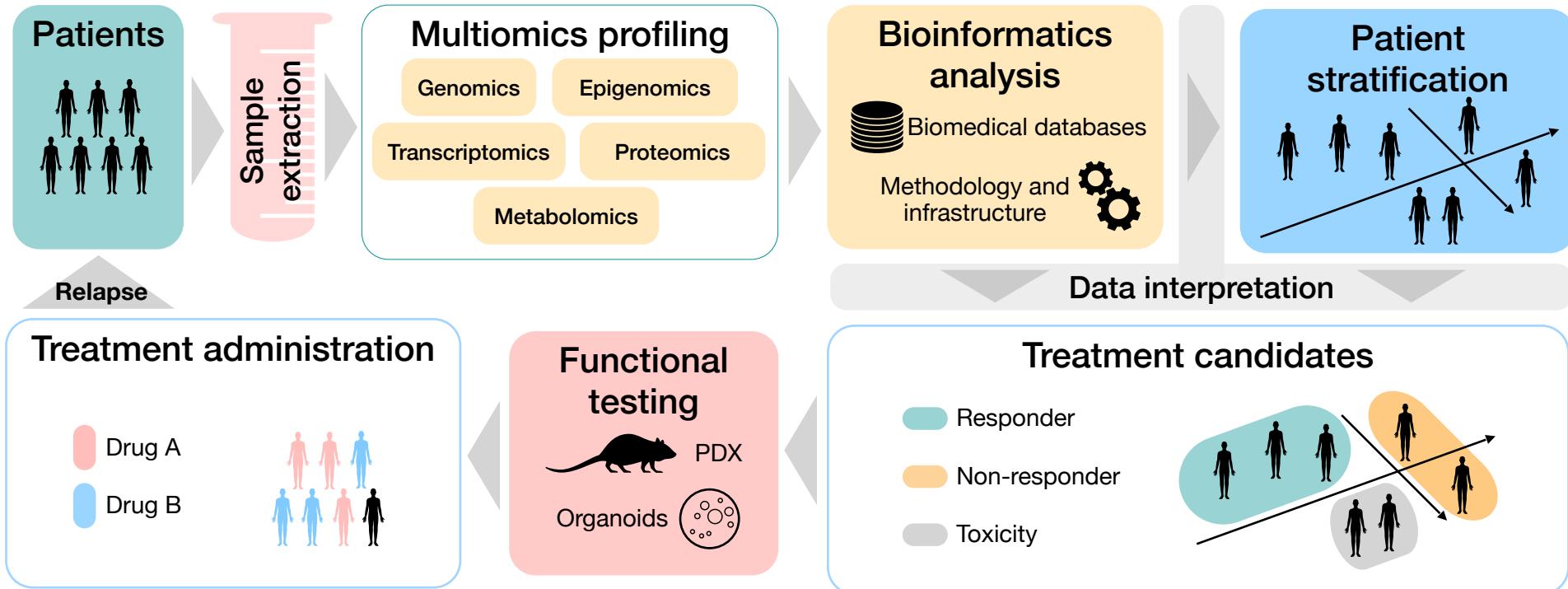


PO21: Precision Oncology Course

PanDrugs: Matching mutations with therapies

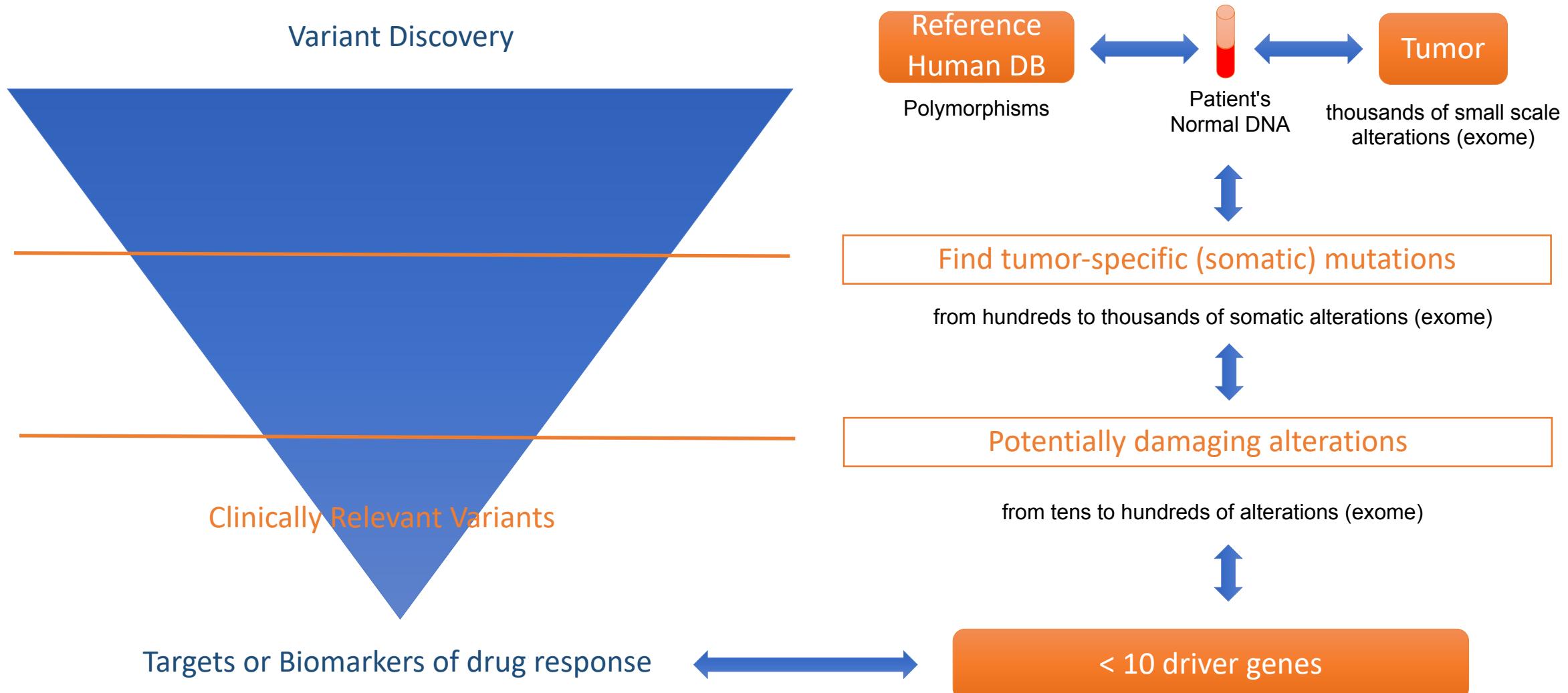
Precision oncology workflow

Identification of the biologically relevant alterations in the patient



The selection the most appropriate therapy according to the individual molecular profile

Genomic profiling through high-throughput screening



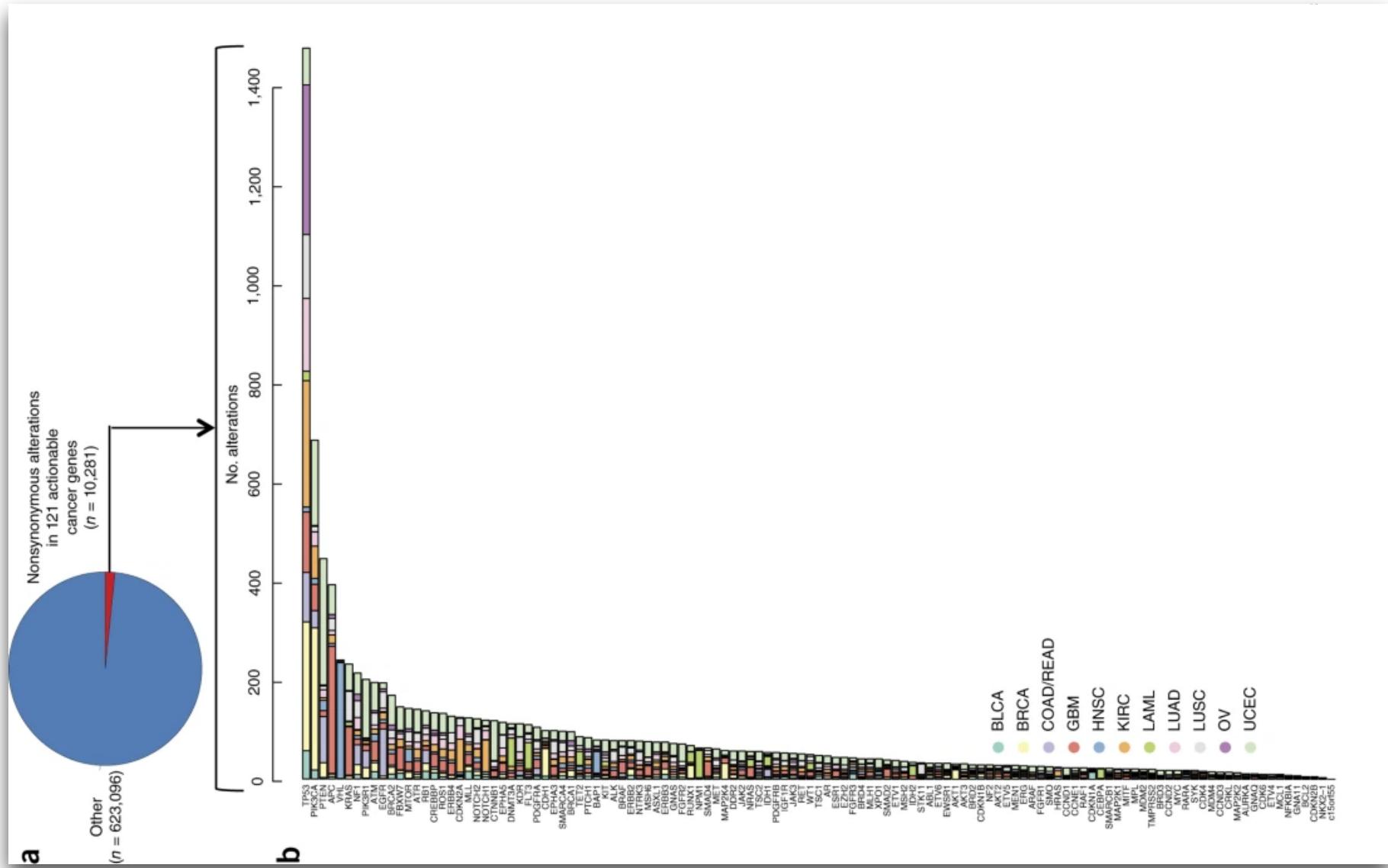
Molecular biomarkers for drug response and targeted therapies

Biomarkers	Number of drugs	Examples
ALK	7	Alectinib, Brigatinib, Ceritinib, Lorlatinib
BCR-ABL1	6	Bosutinib, Dasatinib, Nilotinib, Ponatinib
BRAF	6	Binimetinib, Cobimetinib, Dabrafenib, Encorafenib
BRCA	3	Talazoparib, Olaparib
Chromosome 17p	1	Ibrutinib
EGFR	8	Atezolizumab, Pembrolizumab, Afatinib, Dacomitinib
ERBB2	14	Talazoparib, Olaparib, Neratinib, Pertuzumab
ESR	14	Olaparib, Everolimus, Alpelisib, Fulvestrant
FGFR	1	Erdafitinib
FIP1L1-PDGFR α	1	Imatinib
FLT3	2	Gilteritinib, Midostaurin
IDH1	1	Ivosidenib
IDH2	1	Enasidenib
IL2RA	1	Denileukin Diftitox
KIT	1	Imatinib
Microsatellite Instability	4	Pembrolizumab, Ipilimumab, Lenvatinib, Nivolumab
Mismatch Repair	4	Pembrolizumab, Ipilimumab, Lenvatinib, Nivolumab
MS4A1	1	Rituximab
NTRK	2	Larotrectinib, Entrectinib
PD-L1	2	Atezolizumab, Pembrolizumab
PDGFR β	1	Imatinib
PGR	9	Olaparib, Fulvestrant, Lapatinib, Anastrozole
PIK3CA	1	Alpelisib
PML-RARA	2	Arsenic Trioxide, Tretinoin
RAS	3	Cetuximab, Panitumumab, Regorafenib
ROS1	2	Crizotinib, Entrectinib
TNFRSF8	1	Brentuximab Vedotin

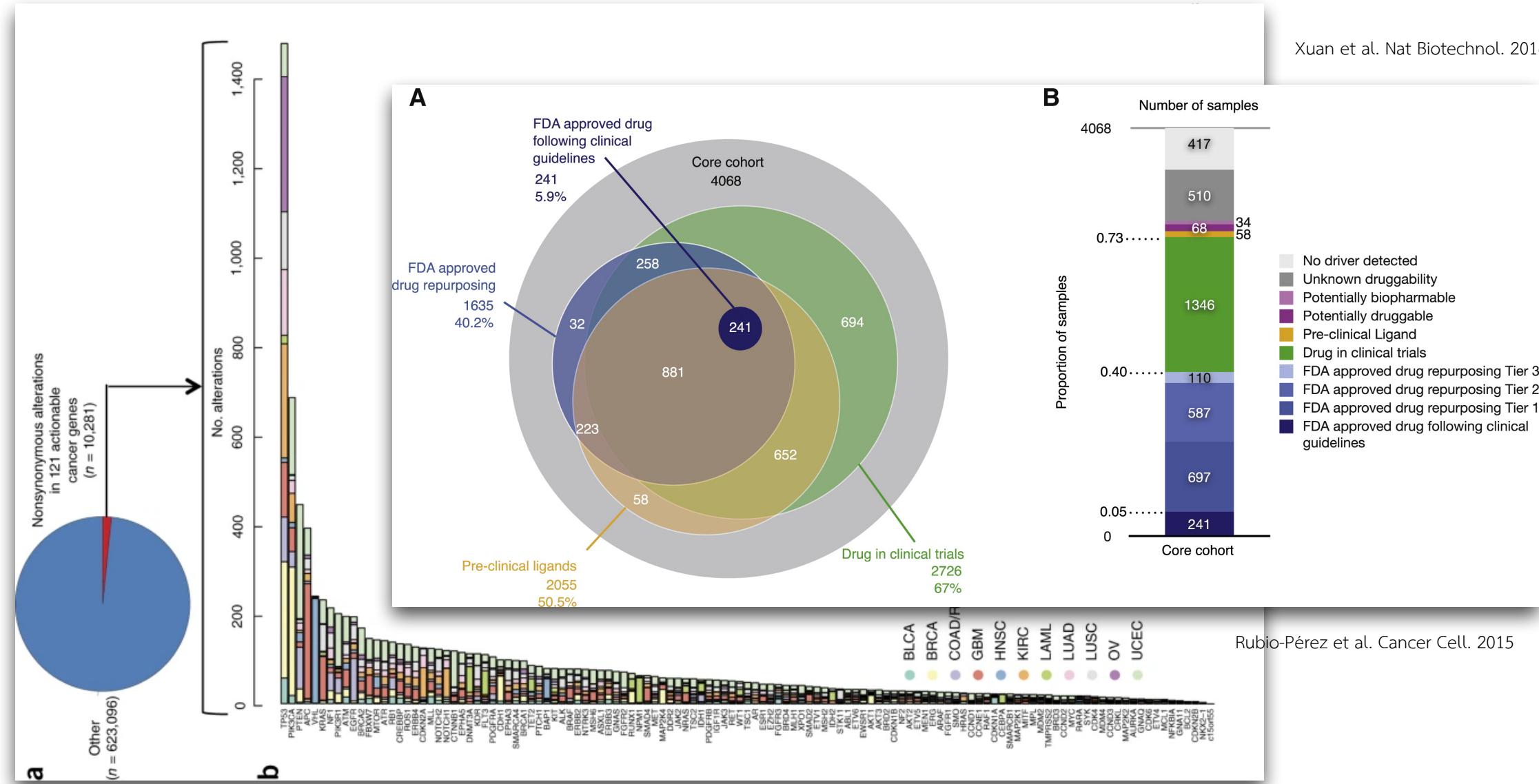
Biomarkers for drug indication in FDA labelling

64 anticancer therapies
linked to
27 biomarkers

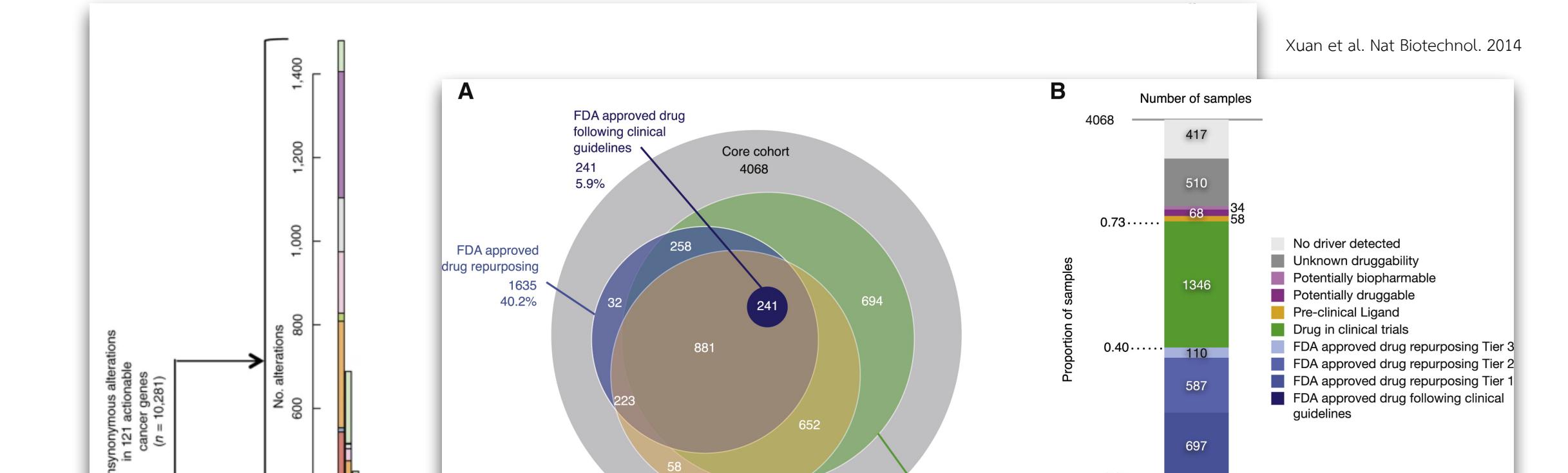
Landscape of actionable cases with cancer treatment guidelines



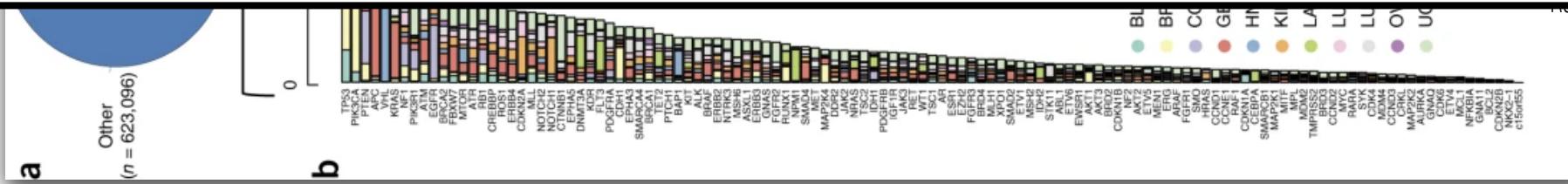
Landscape of actionable cases with cancer treatment guidelines



Landscape of actionable cases with cancer treatment guidelines



It is necessary to expand the therapeutic options



In silico drug prescription in cancer

PANDRUGS

Home Query PanDrugs in TCGA API Help Login

version: 2018.11.7

Welcome to
PANDRUGS
A novel method for prioritizing therapies using individual
genomic data

Query! ✓

What is PanDrugs?

PanDrugs provides a bioinformatics platform to prioritize anticancer drug treatments according to individual genomic data. PanDrugs current version integrates data from 24 primary sources and supports 56297 drug-target associations obtained from 4804 genes and 9092 unique compounds.

Data input: standard VCF file, RNK file, gene lists and drug query.

Please note the PanDrugs terminology for druggable genes:

- I. **Direct targets:** Genes that contribute to disease phenotype and can be directly targeted by a drug (e.g. BRAF is a direct target for vemurafenib).
- II. **Biomarkers:** Genes showing a genetic status associated with drug response which protein product is not the drug target itself (e.g. BRCA-mutated cancers responding to PARP inhibitors).
- III. **Pathway members:** Genes located downstream in the biological pathway of a given undruggable gene (e.g. patients with mutations in TSC1/2 respond to a downstream inhibition of the mTOR pathway).



DIRECT TARGET



BIOMARKER



PATHWAY MEMBER

SING
Upgrading your knowledge



www.pandrugs.org

Piñeiro-Yáñez, E, Reboiro-Jato M et al. Genome Medicine. 2018

Database - Drug-gene associations

Confidence level

Source	Source provider	# initial records	# processed records	Direct Target /Biomarker	Sensitivity/Resistance	Alteration type	Expert curated
CancerCommons	DGIdb	104	104	yes			yes
CGI	DGIdb	309	309	yes	yes	yes	yes
ChEMBLInteractions	DGIdb	7695	7558				
CIViC	DGIdb	534	534		yes	yes	yes
CKB	DGIdb	1412	1403		yes	yes	yes
ClearityFoundationBiomarkers	DGIdb	148	148	yes	yes	yes	yes
ClearityFoundationClinicalTrial	DGIdb	178	175				yes
DoCM	DGIdb	72	72		yes	yes	yes
DrugBank	DGIdb	7805	7723	yes			
FDA	DGIdb	245	244	yes	yes	yes	yes
GuideToPharmacologyInteractions	DGIdb	7672	7613	yes			yes
MyCancerGenome	DGIdb	814	782	yes	yes		yes
MyCancerGenomeClinicalTrial	DGIdb	319	303		yes		yes
NCI	DGIdb	4298	4287	yes	yes	yes	yes
Oncokb	DGIdb	155	155			yes	yes
PharmGKB	DGIdb	1274	1245				
TALC	DGIdb	492	486	yes	yes		yes
TdgClinicalTrial	DGIdb	4155	4085	yes			yes
TTD	DGIdb	1829	2210	yes			
TEND	DGIdb	2233	1822	yes			yes
moAb	moAb	605	605	yes			yes
TARGET-CGA	TARGET	74	72	yes	yes	yes	yes
CTRP	CTRP	397270	13041		yes		
GDSC	GDSC	1323	1321		yes		
TOTAL		441015	36297				

Preclinical studies

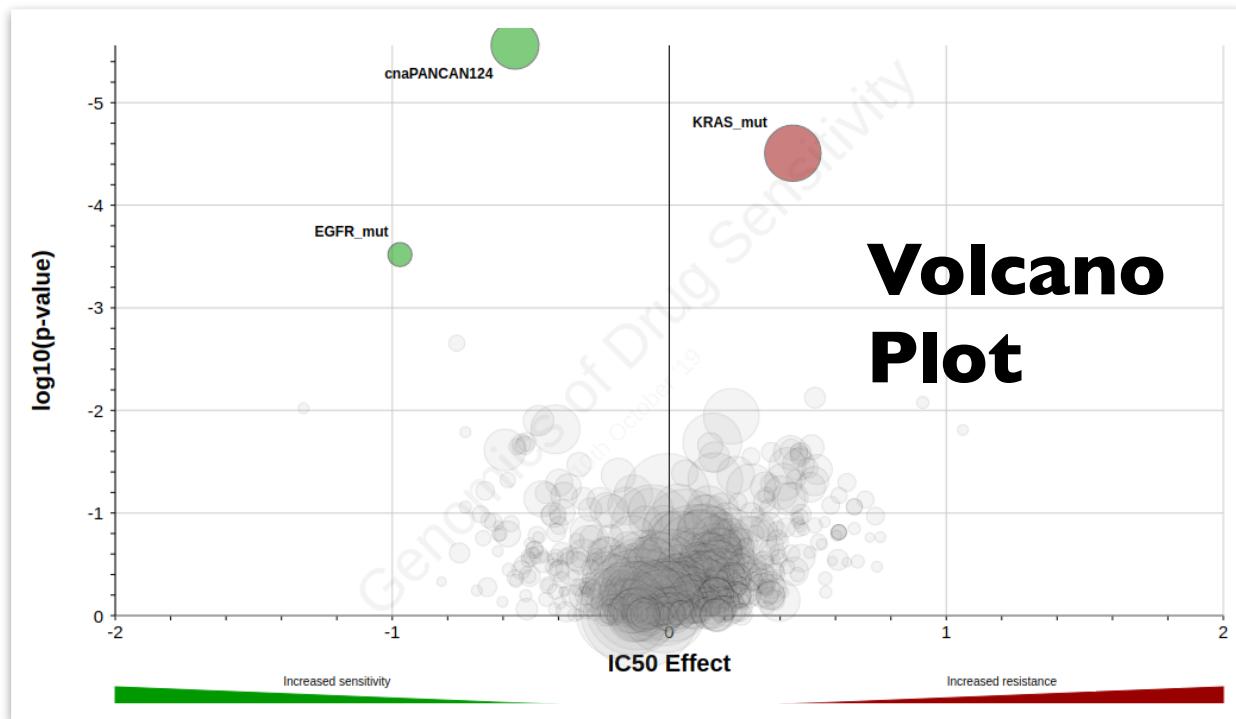
Drug-gene association resources: GDSC

~ 1000 cancer cell lines
with genomic information
about mutations,
amplifications, deletions,
rearrangements

320 compounds

<http://www.cancerrxgene.org/>

Gefitinib: EGFR targeted therapy



Cancer feature	Known Driver Genes	Effect size	P-value	FDR%	No. of altered cell lines	Tissue analysis
cnaPANCAN124	EGFR	-0.557	2.76e-06	0.166	79	PANCANCER
KRAS_mut	-	0.446	3.11e-05	0.932	110	PANCANCER
EGFR_mut	-	-0.972	0.000303	6.05	20	PANCANCER
EPHA2_mut	-	-0.767	0.00221	33.1	9	PANCANCER
cnaPANCAN7	SMARCA4	0.526	0.00751	61.2	15	PANCANCER
VHL_mut	-	0.915	0.00838	61.2	5	PANCANCER
cnaPANCAN100	-	-1.32	0.00953	61.2	4	PANCANCER
cnaPANCAN368	-	0.224	0.0114	61.2	107	PANCANCER
cnaPANCAN58	-	-0.472	0.0126	61.2	32	PANCANCER
MLL2_mut	-	-0.411	0.0153	61.2	83	PANCANCER

Drug-gene association resources: CTRP

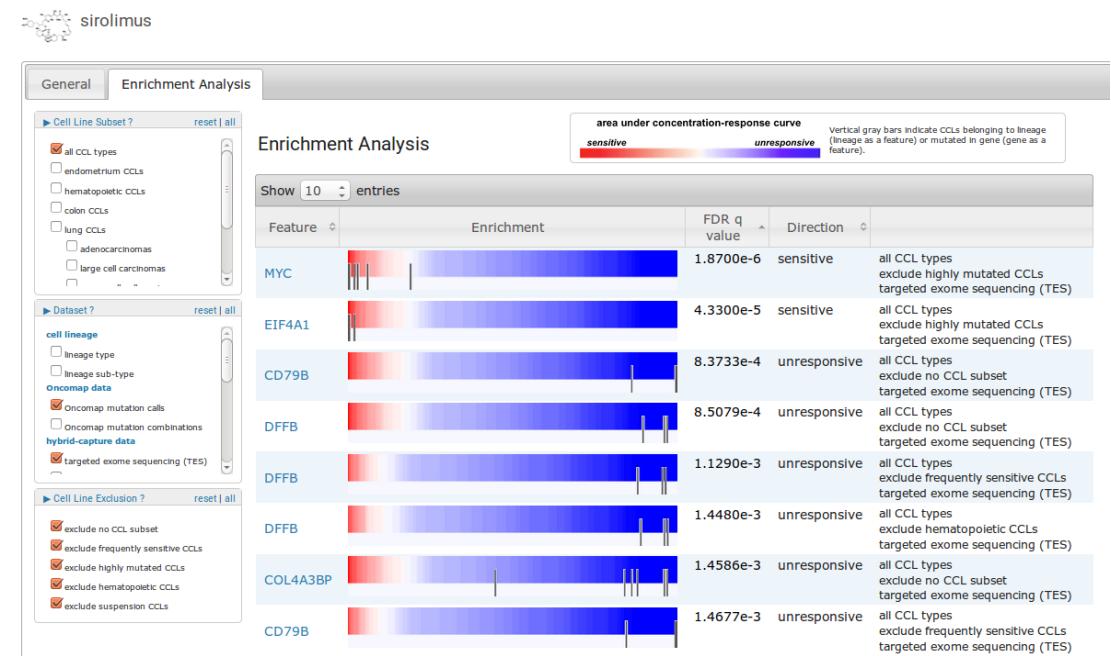
The screenshot shows the Cancer Therapeutics Response Portal (v1) interface. At the top, there is a navigation bar with icons for COMPOUNDS, FEATURES, and TARGETS. The main content area displays a table with one entry for 'sirolimus'. The table columns include Structure, Name, Synonyms, Targets, Status, and starting assay concentration (uM). The entry for sirolimus is shown with its chemical structure, name 'sirolimus', synonyms 'rapamycin; Rapamune', target 'inhibitor of mTOR via FRB domain (in complex with FKBP)', status 'FDA-approved', and concentration '37 uM'. A search bar at the top right allows for searching 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 | Next | Last

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

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

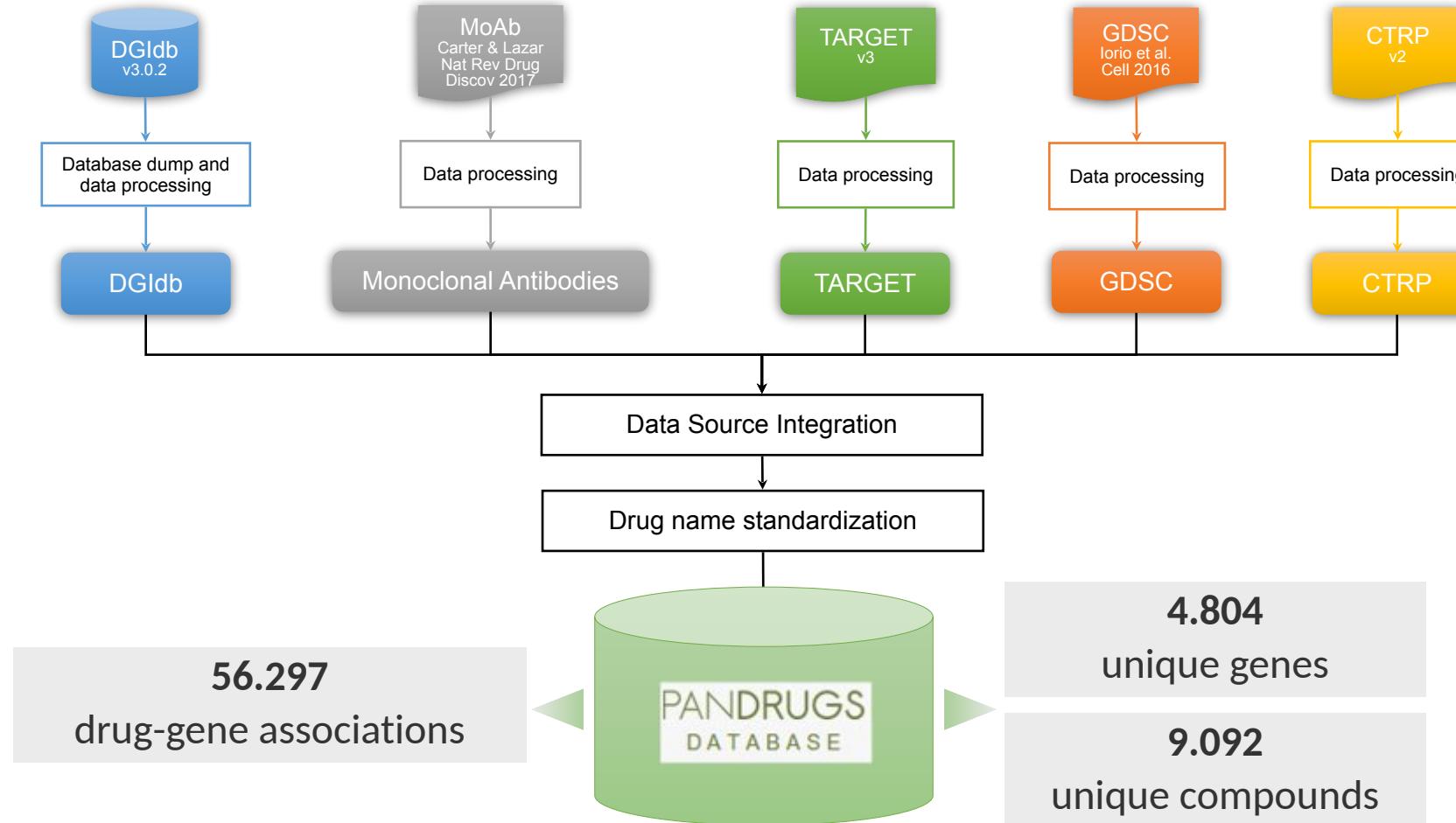


Database - Drug-gene associations

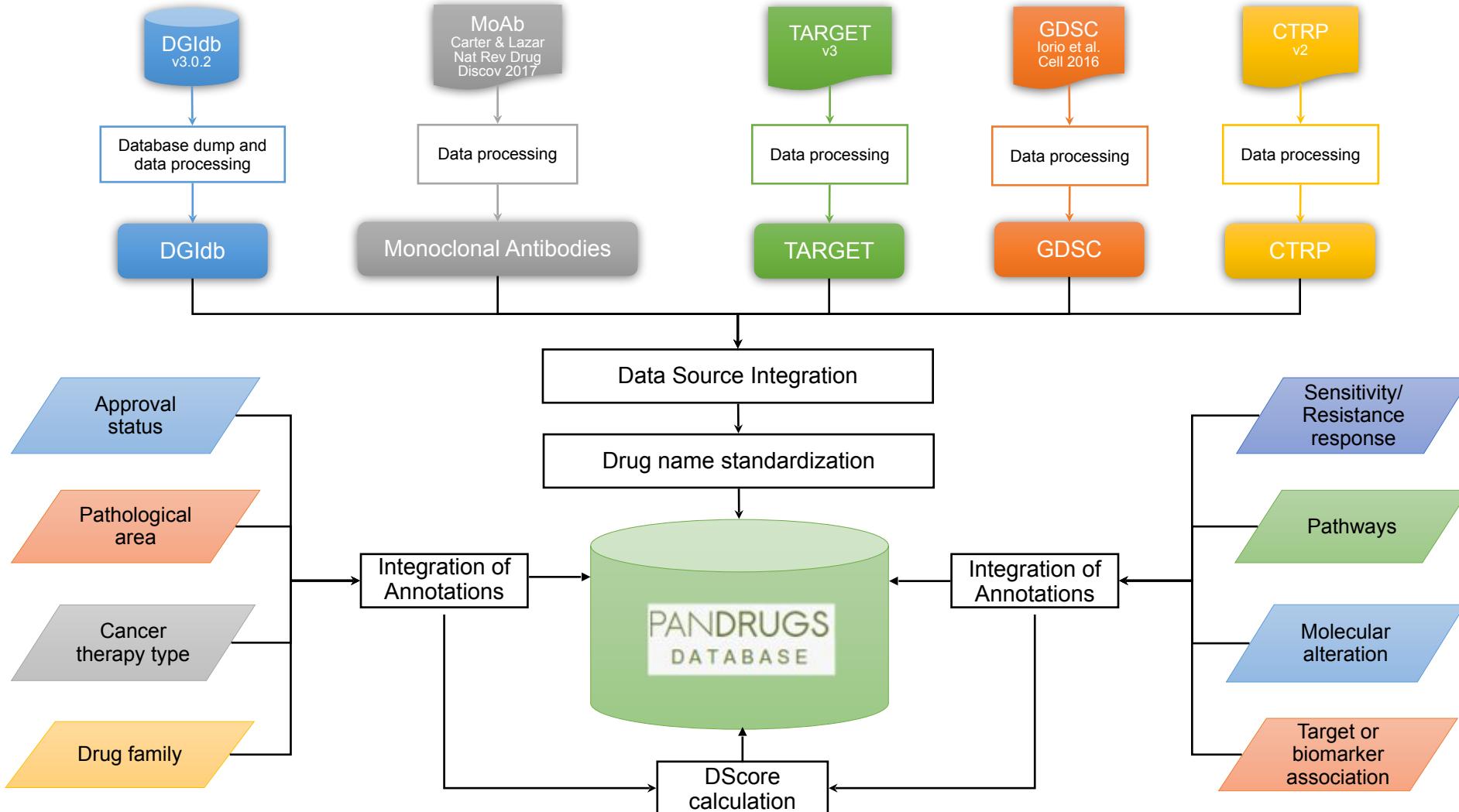
Association with the gene

Source	Source provider	# initial records	# processed records	Direct Target /Biomarker	Sensitivity/Resistance	Alteration type	Expert curated
CancerCommons	DGIdb	104	104	yes			yes
CGI	DGIdb	309	309	yes	yes	yes	yes
ChEMBLInteractions	DGIdb	7695	7558				
CIViC	DGIdb	534	534		yes	yes	yes
CKB	DGIdb	1412	1403		yes	yes	yes
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ClearityFoundationClinicalTrial	DGIdb	178	175				yes
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GuideToPharmacologyInteractions	DGIdb	7672	7613	yes			yes
MyCancerGenome	DGIdb	814	782	yes	yes		yes
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Oncokb	DGIdb	155	155			yes	yes
PharmGKB	DGIdb	1274	1245				
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TdgClinicalTrial	DGIdb	4155	4085	yes			yes
TTD	DGIdb	1829	2210	yes			
TEND	DGIdb	2233	1822	yes			yes
moAb	moAb	605	605	yes			yes
TARGET-CGA	TARGET	74	72	yes	yes	yes	yes
CTRP	CTRP	397270	13041		yes		
GDSC	GDSC	1323	1321		yes		
Total		441015	56297				

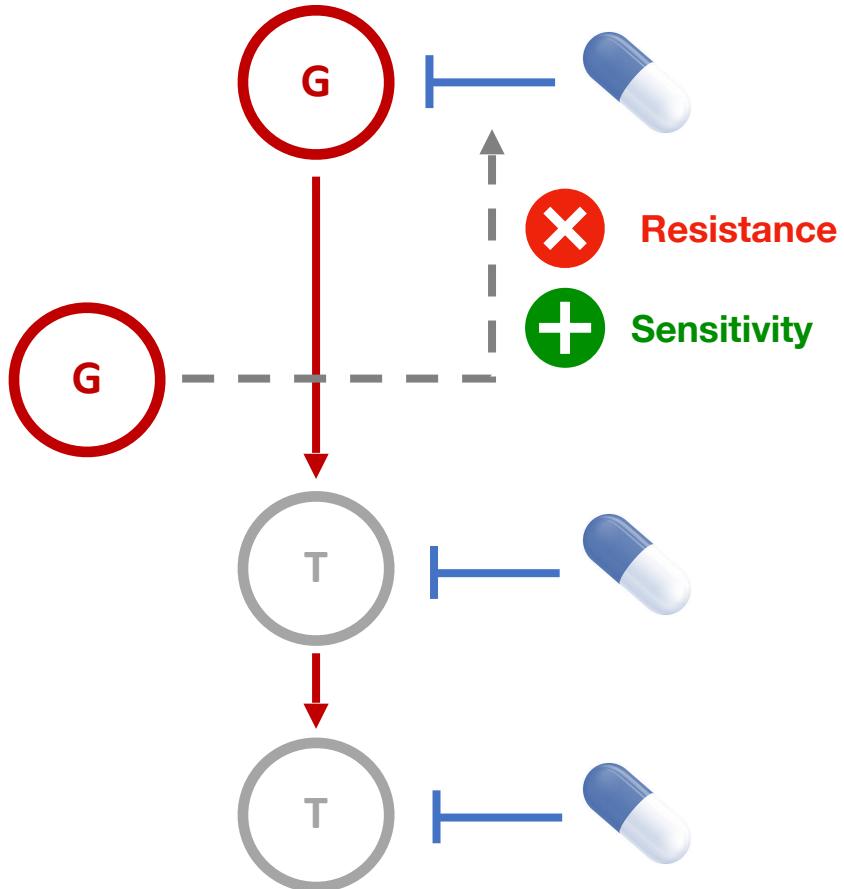
PanDrugs database



PanDrugs database

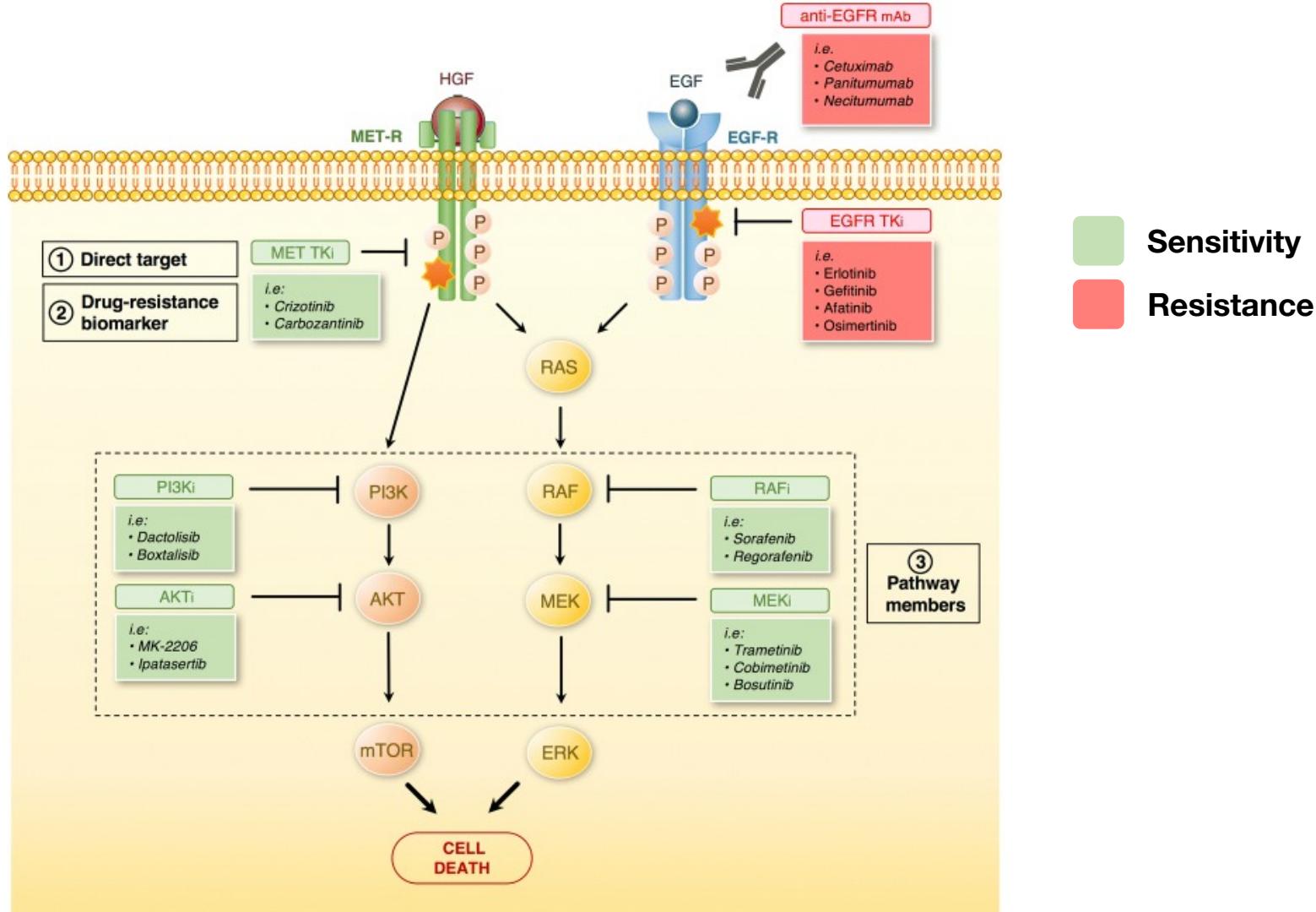


Therapy search logic

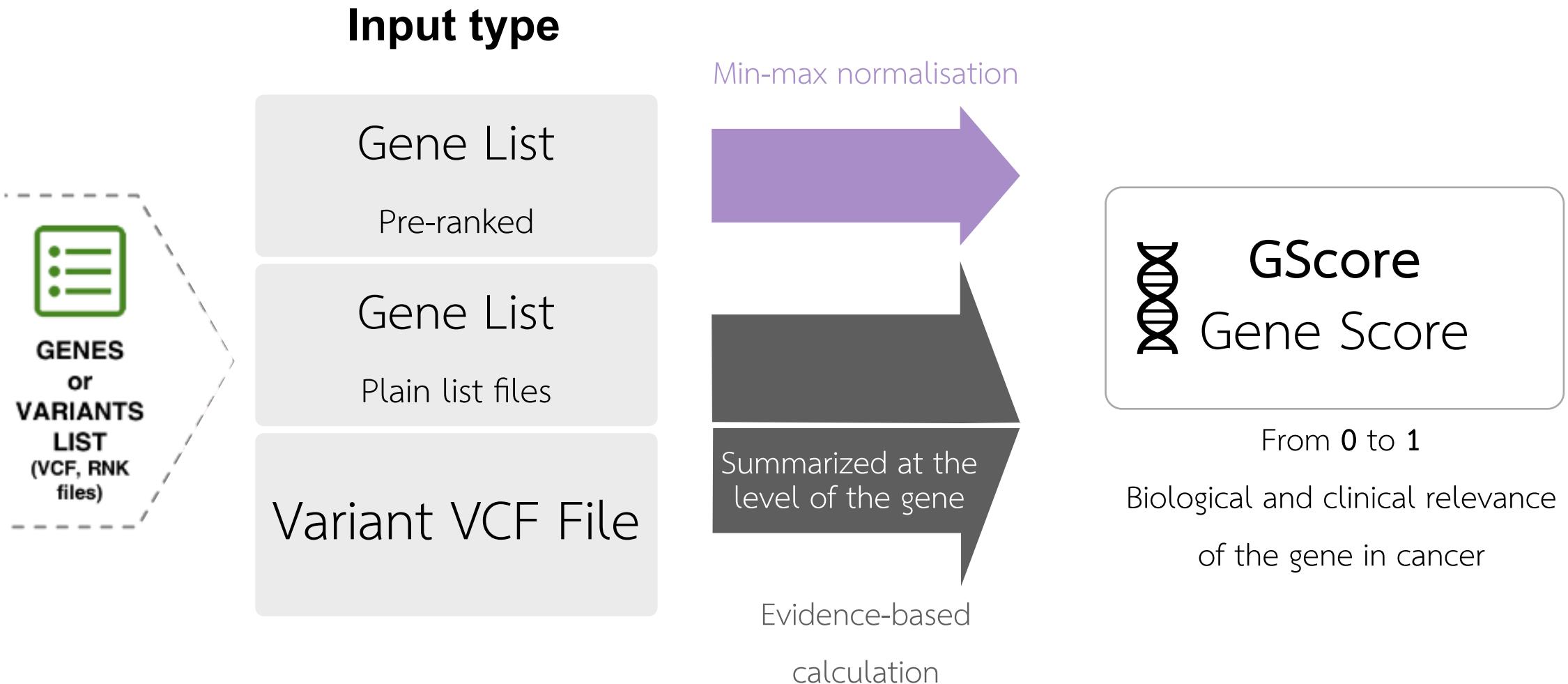


- 1 DIRECT TARGET**
The gene contributes to a disease phenotype and can be **directly targeted by a drug**
- 2 BIOMARKER**
The gene product is not the **direct target of the drug**, but the gene status is **associated with a drug response** from clinical or pre-clinical evidence
- 3 PATHWAY MEMBER**
The targetable gene is located **downstream** to the altered one

Therapy search logic



Prioritization system for individual genomic alterations



Evidence for plain list of genes

Feature	Weight	Value	Score
Essentiality Score	40%	Computed Essentiality Score	[0 - 1]
OncoScape Score	30%	max{max{OncoScape score for oncogene in different tumor types}, max{OncoScape score for tumor suppressor gene in different tumor types}} normalized between 0 and 1	[0 - 1]
Gene annotated in TumorPortal	10%	Highly significantly mutated	1
		Significantly mutated	0.5
		Near significance	0.25
		No annotation	0
Gene annotated in Cancer Gen Census (COSMIC)	10%	Yes	1
		No	0
Driver Gene	10%	High confidence driver	1
		Candidate driver	0.5
		No annotation	0

Evidence for a variant VCF file

VEP ensembl				VCF annotation			
Additional annotations				Cancer specific annotations			
Feature	Value	Weight ONC	Weight TSG	Feature	Value	Weight ONC	Weight TSG
Polyphen	> 0.435	+ 0.125 / 3	+ 0.125 / 3	1000 genomes GMAF	< 1	+ 0.125 / 2	+ 0.125 / 2
Sift	<= 0.05	+ 0.125 / 3	+ 0.125 / 3	ExAC AF	< 1	+ 0.125 / 2	+ 0.125 / 2
Condel	> 0.468	+ 0.125 / 3	+ 0.125 / 3	Zygoty	Homozygous	+ 0.125	+ 0.1875
VEP consequence	stop gain frameshift missense inframe insertion inframe deletion	+ 0.125	+ 0.125	Mutation frequency in COSMIC	>= 100	+ 0.125 / 3	
Domains	Listed as relevant in cancer or previous last protein domain (stop gain or frameshift)	+ 0.125	+ 0.125		< 100	+ 0.125 / 3 (log (mutation frequency) / log (max mutation frequency))	
	Within a domain in other circumstances	+ 0.125 / 2	+ 0.125 / 2	Gene alteration frequency in COSMIC	>= 100	+ 0.125 / 3	+ 0.03125
ClinVar	Pathogenic with zygosity data	+ 0.125	+ 0.125		< 100	+ 0.125 / 3 * (log (gene frequency) / log (max gene frequency))	+ 0.03125 * (log (gene frequency) / log (max gene frequency))
	Pathogenic without zygosity data	+ 0.250	+ 0.3125	COSMIC FATHMM	Pathogenic	+ 0.125 / 3	+ 0.03125
Essentiality Score		+ 0.125 * ES	+ 0.125 * ES				

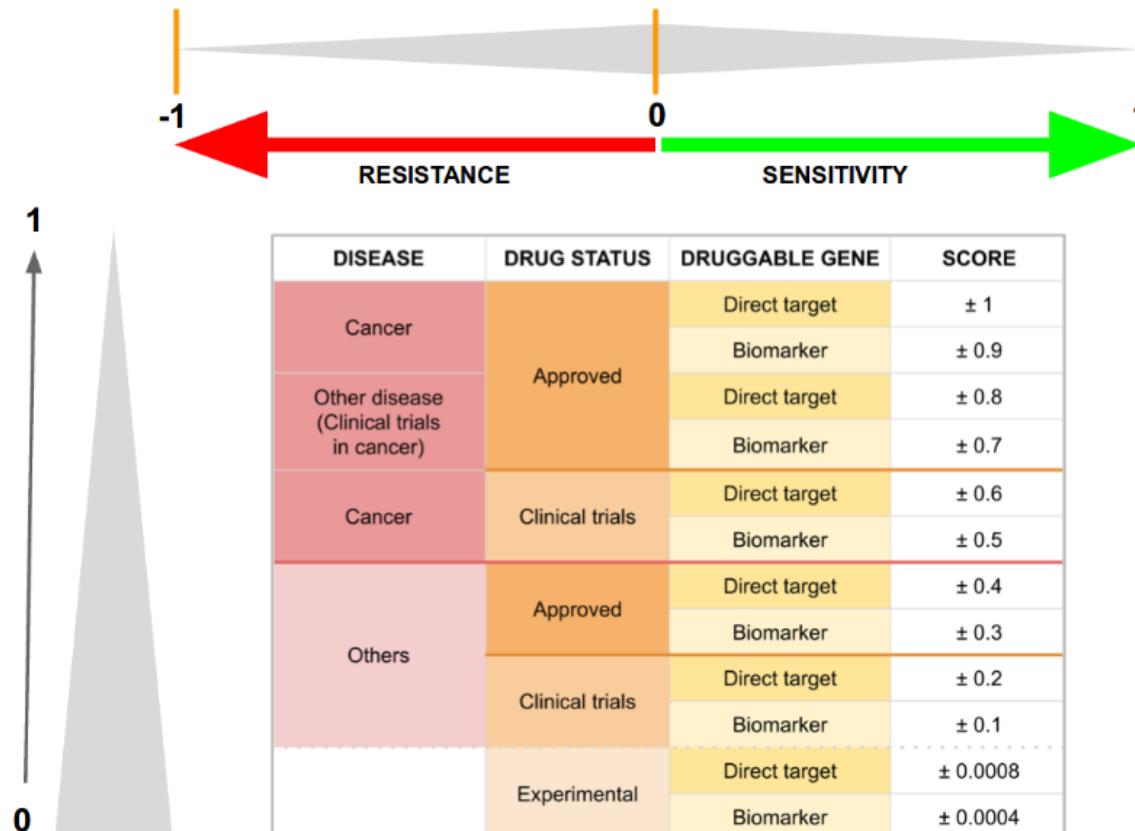
Prioritization system for therapies



From -1 to 1

Suitability of the therapy in the
genomic context

Pre-computed DScore in PanDrugsdb



Prioritization system for therapies

Adjustment of pre-computed DScore based on collective evidence:

Approved and Clinical trials drugs:

- **Pre-computed DScore value** = [Cancer + Drug Status + Druggable gene type]*[if *resistance* (-1)]
- **Collective gene impact** = # genes (max. 9) + [-1(if *pathway member*)]
- **Database factor** = # expert curated sources (max. 9)

DScore = max{Pre-computed DScore value} - 0.1 + (0.01 * Collective gene impact) + 0.001 + (0.001 * Database factor)

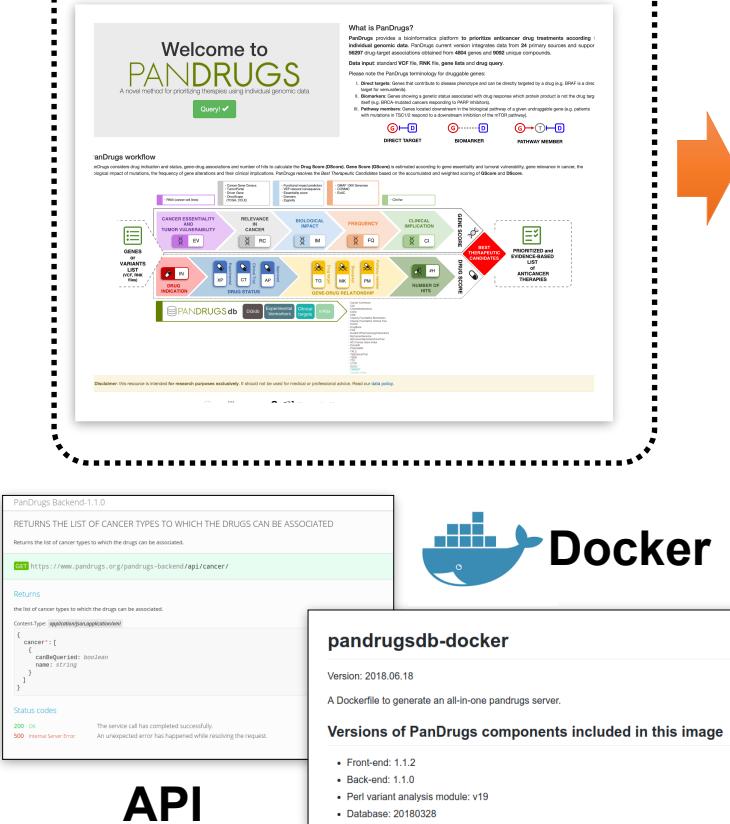
Experimental:

DScore = max{Pre-computed DScore value} - 0.0002 (if *indirect*)

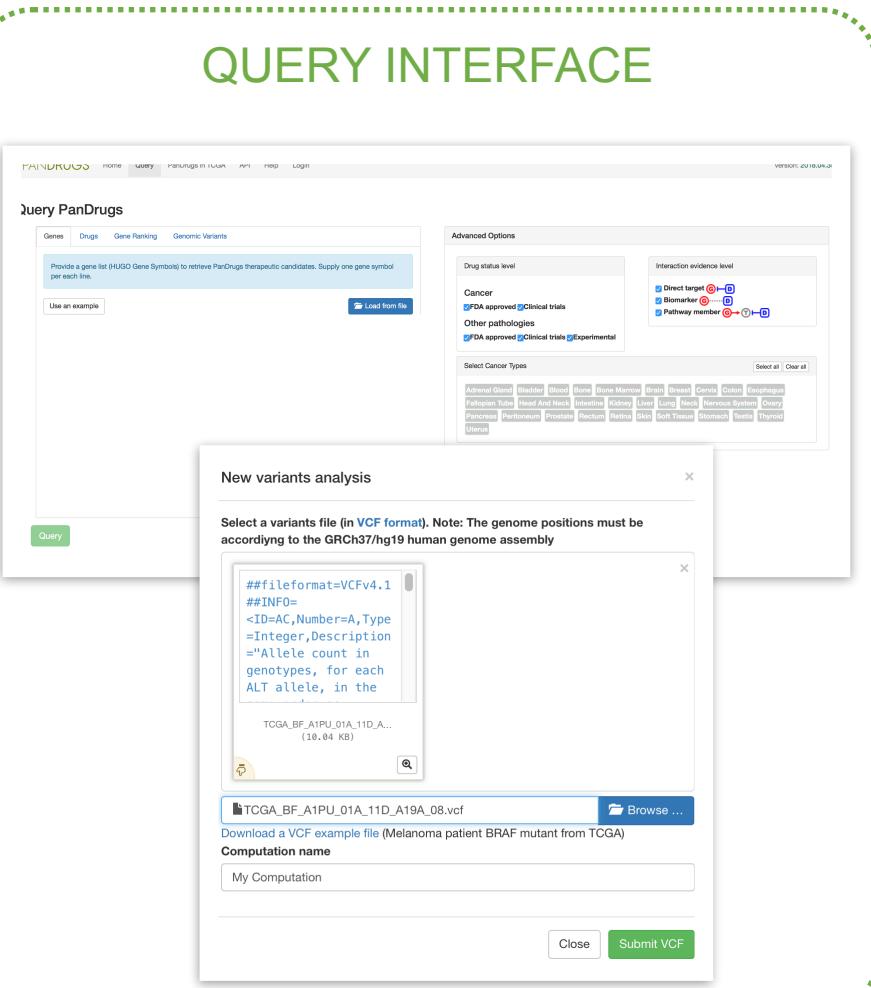
PanDrugs interface



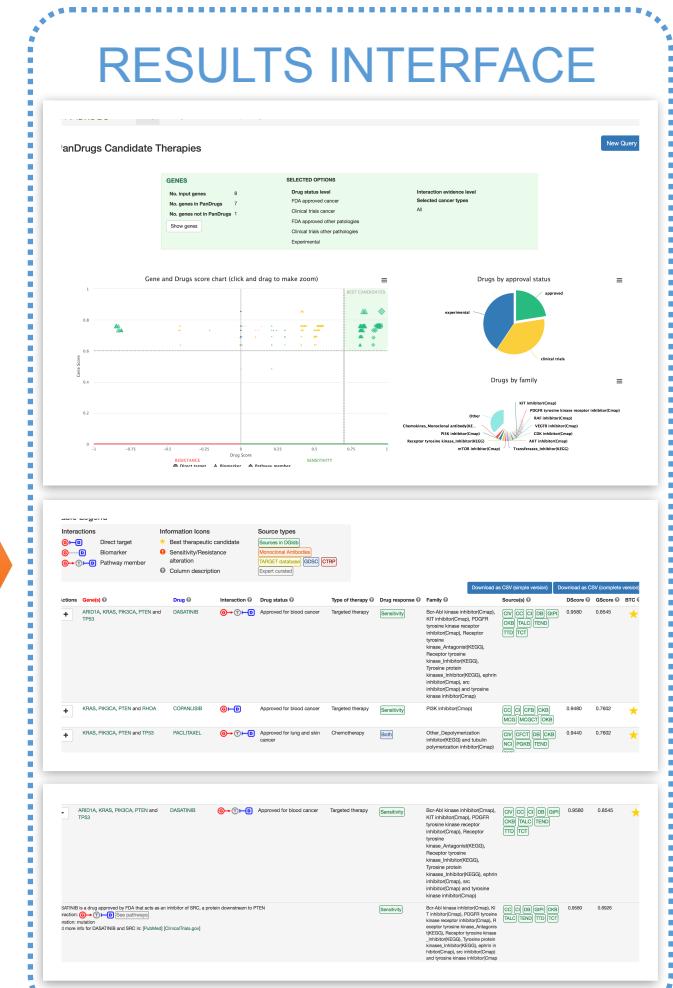
MAIN INTERFACE



QUERY INTERFACE



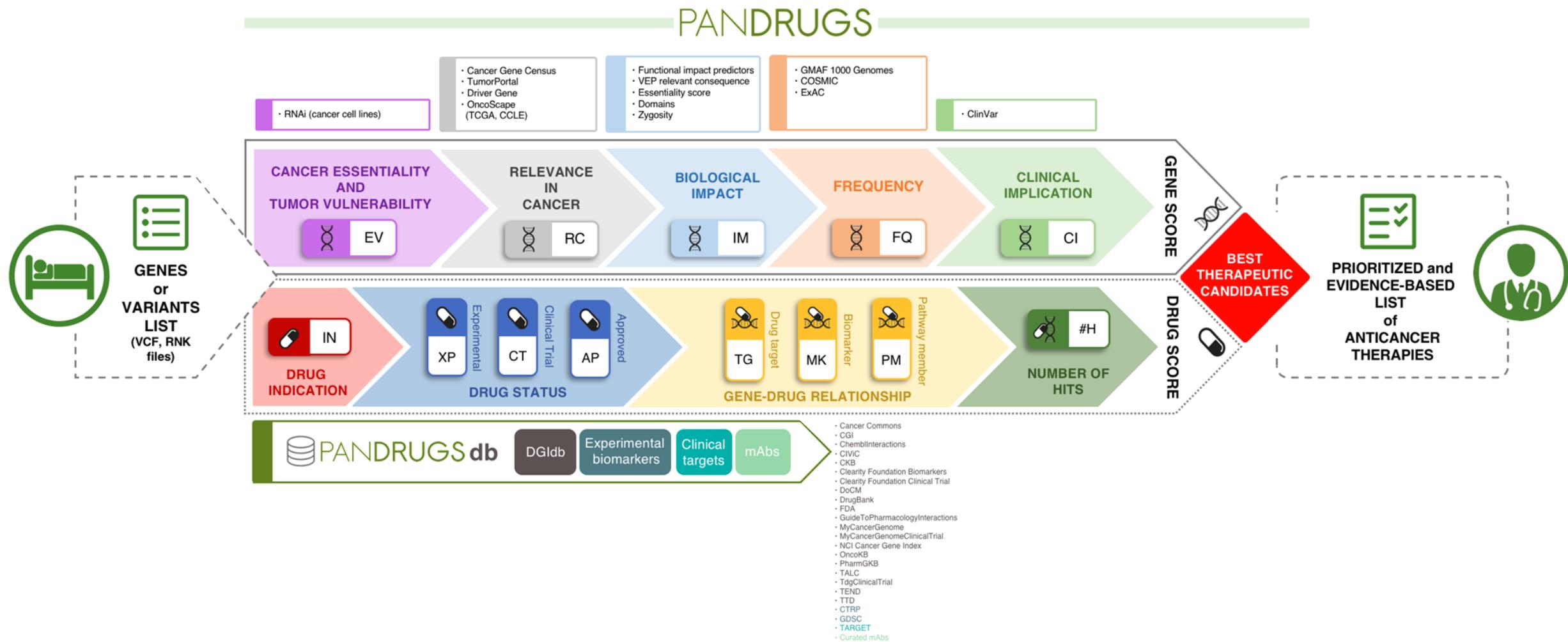
RESULTS INTERFACE



Workflow



www.pandrugs.org

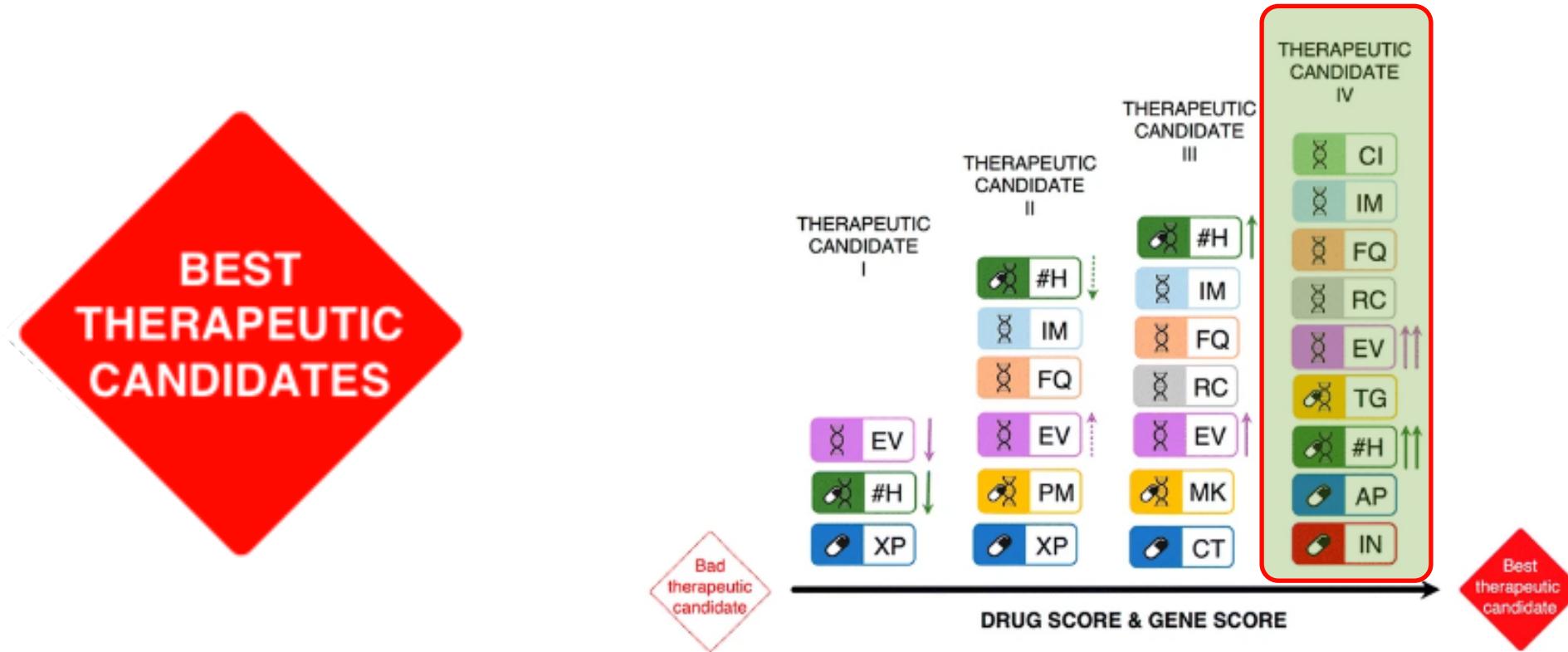


Workflow



www.pandrugs.org

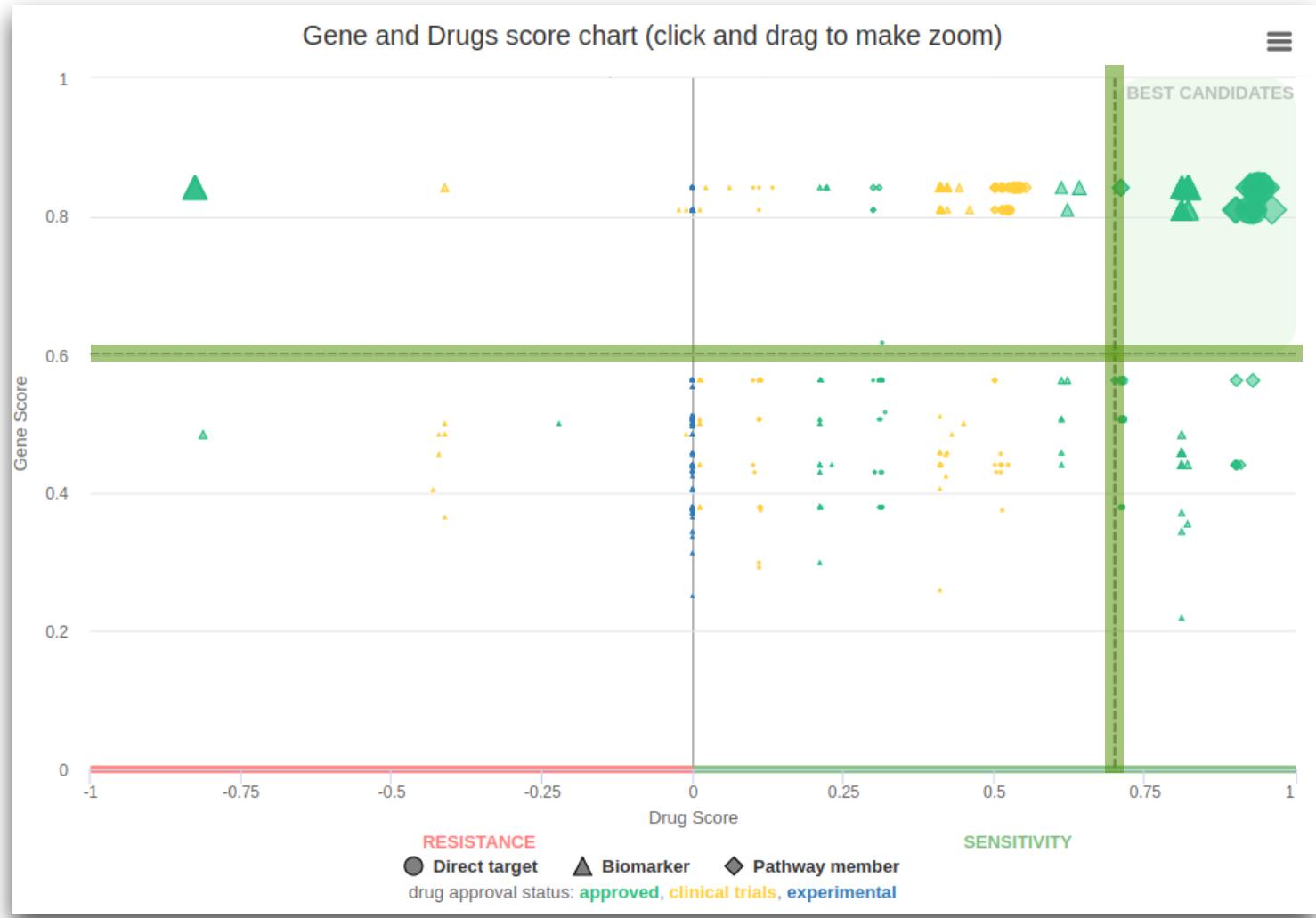
Best therapeutic candidates are most suitable drugs that act on most relevant genes in the particular case



Output



www.pandrugs.org



Experience and TCGA
systematic application



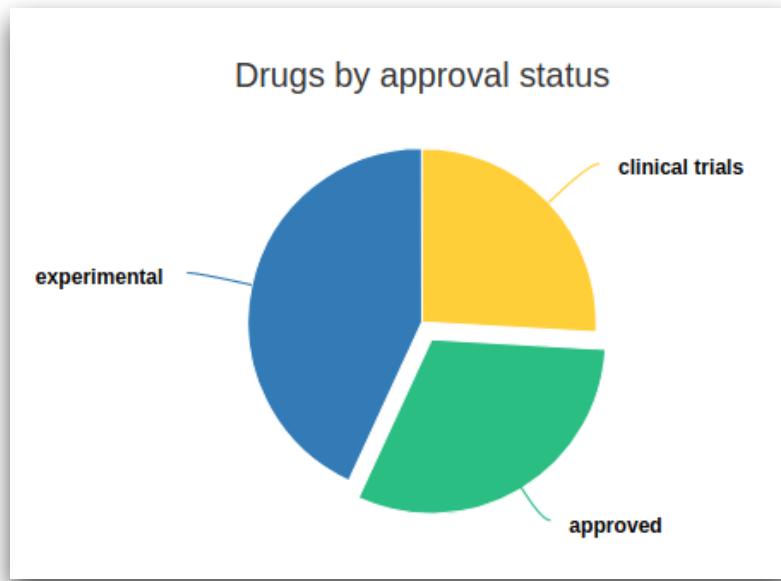
Approved compounds in
cancer or in other pathologies
enrolled in cancer clinical
trials

Output

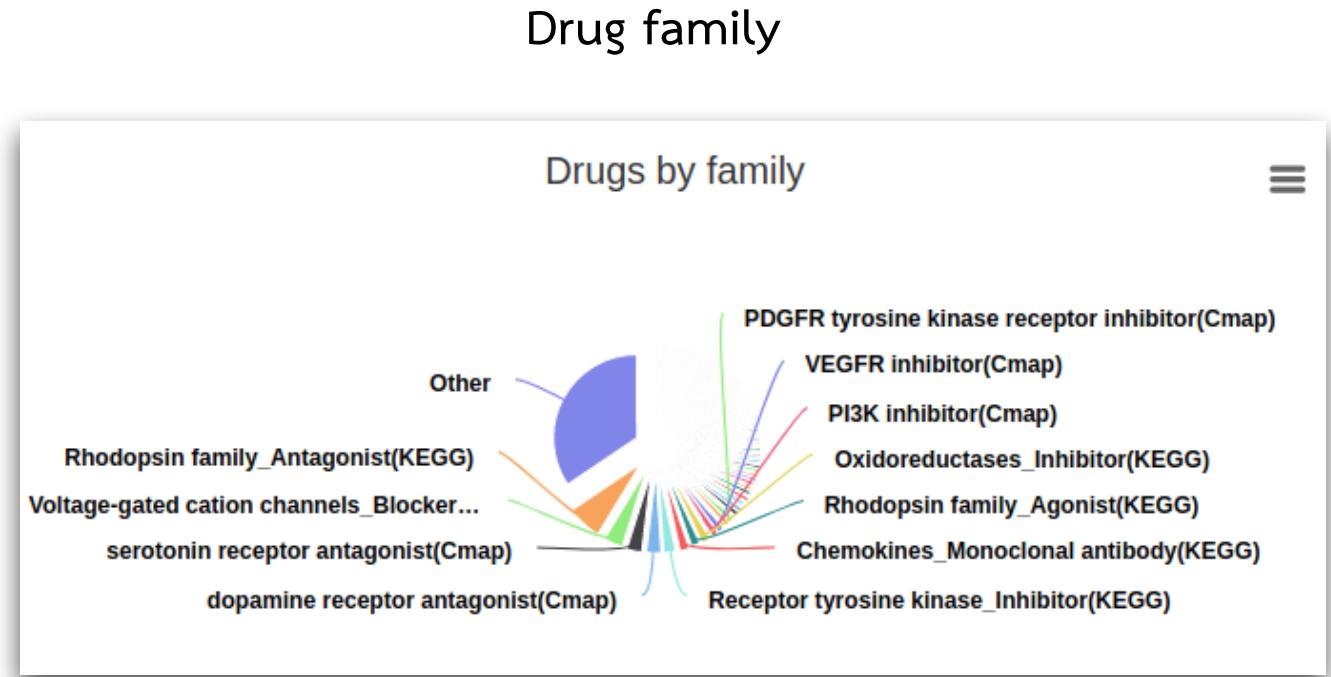


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Summary of the proposed drugs



Approval status



Output



www.pandrugs.org

Action	Gene(s)	Drug	Interaction	Drug status	Type of therapy	Drug response	Family	Source(s)	DScore	GScore	BTC
	BLM, BRAF, CPAMD8, EPHB6, PAX5 and TTBK1	BORTEZOMIB		Approved for blood cancer	Targeted therapy	Both	Hydrolases_Inhibitor(KEGG), NFkB pathway inhibitor(Cmap) and proteasome inhibitor(Cmap)		0.9620	0.8091	
	BRAF, COL1A1, NTRK1 and PTEN	DASATINIB		Approved for blood cancer	Targeted therapy	Sensitivity	Bcr-Abl kinase inhibitor(Cmap), KIT inhibitor(Cmap), PDGFR tyrosine kinase receptor inhibitor(Cmap), Receptor tyrosine kinase_Antagonist(KEGG), Receptor tyrosine kinase_Inhibitor(KEGG), Tyrosine protein kinases_Inhibitor(KEGG), ephrin inhibitor(Cmap), src inhibitor(Cmap) and tyrosine kinase inhibitor(Cmap)	 	0.9500	0.8414	

Output



www.pandrugs.org

Actions **G** **B** **+** **+** **+**

BLM, BRAF, CPAMD8, EPHB6, PAX5 and TTBK1	BORTE ZOMIB		Approved for blood cancer	Targeted therapy	Both	Hydrolases_Inhibitor(KEGG), NFkB pathway inhibitor(Cmap) and proteasome inhibitor(Cmap)	CTRPA TALC	0.9620	0.8091	★					
BORTEZOMIB is a drug approved by FDA that acts as an inhibitor of BCL2, a protein downstream to BRAF Interaction: See pathways										Sensitivity					
Find more info for BORTEZOMIB and BCL2 in: [PubMed] [ClinicalTrials.gov]										Hydrolases_Inhibitor(KEGG), N FkB pathway inhibitor(Cmap) a nd proteasome inhibitor(Cmap)	TALC	0.9620	0.8091	★	
Variant information in gene BRAF: c.1799T>A / p.Val600Glu missense variant S P C ClinVar IPR000719: Protein kinase domain										Resistance	Hydrolases_Inhibitor(KEGG), N FkB pathway inhibitor(Cmap) a nd proteasome inhibitor(Cmap)	CTRPA	-0.8610	0.4841	★
Molecular alterations in BLM are associated with response to BORTEZOMIB, a drug approved by FDA Interaction:										Resistance	Hydrolases_Inhibitor(KEGG), N FkB pathway inhibitor(Cmap) a nd proteasome inhibitor(Cmap)	CTRPA	-0.8610	0.4553	★
Find more info for BORTEZOMIB and BLM in: [PubMed] [ClinicalTrials.gov]										IPR014001: Helicase superfamily 1/2, ATP-binding domain					
Variant information in gene BLM: c.2340_2341delinsTT / p.Glu781Ter stop gained S P C IPR014001: Helicase superfamily 1/2, ATP-binding domain										Resistance	Hydrolases_Inhibitor(KEGG), N FkB pathway inhibitor(Cmap) a nd proteasome inhibitor(Cmap)	CTRPA	-0.8610	0.4553	★
Molecular alterations in CPAMD8 are associated with response to BORTEZOMIB, a drug approved by FDA Interaction:										Resistance	Hydrolases_Inhibitor(KEGG), N FkB pathway inhibitor(Cmap) a nd proteasome inhibitor(Cmap)	CTRPA	-0.8610	0.4553	★
Find more info for BORTEZOMIB and CPAMD8 in: [PubMed] [ClinicalTrials.gov]										COSMIC					
Variant information in gene CPAMD8: c.1442G>A / p.Gly481Glu missense variant P C COSMIC															

complete version) [Score ?](#) [BTC ?](#)

3091 3414

Gene search example - Input

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

EGFR
KRAS
TP53

Load from file

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

Direct target

Biomarker

Pathway member

Select Cancer Types

Select all Clear all

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

Gene search example - Summary

PanDrugs Candidate Therapies

GENES		SELECTED OPTIONS	
No. input genes	3	Drug status level	Interaction evidence level
No. genes in PanDrugs	3	FDA approved cancer	Selected cancer types
No. genes not in PanDrugs	0	Clinical trials cancer	All
Show genes			

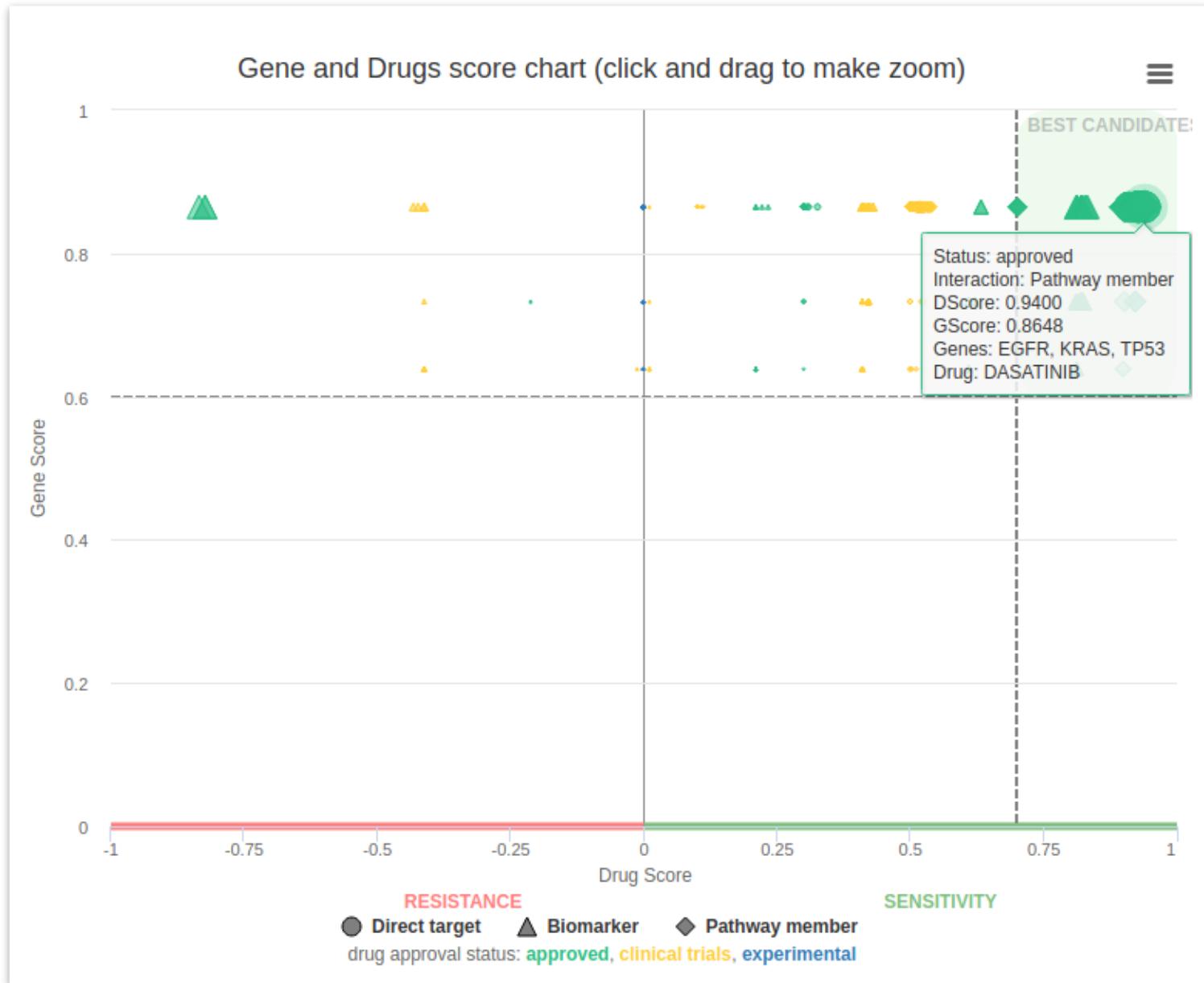
Genes in query ×

Input genes (3)
EGFR, KRAS and TP53

Genes in PanDrugs (3)
KRAS, TP53 and EGFR

Genes not in PanDrugs (0)

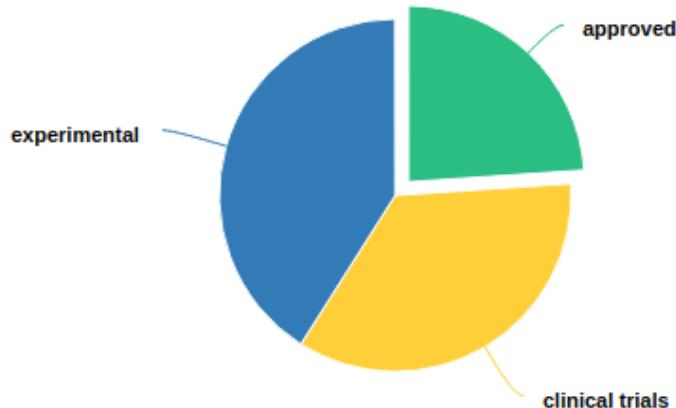
Gene search example - Representations



Gene search example - Representations

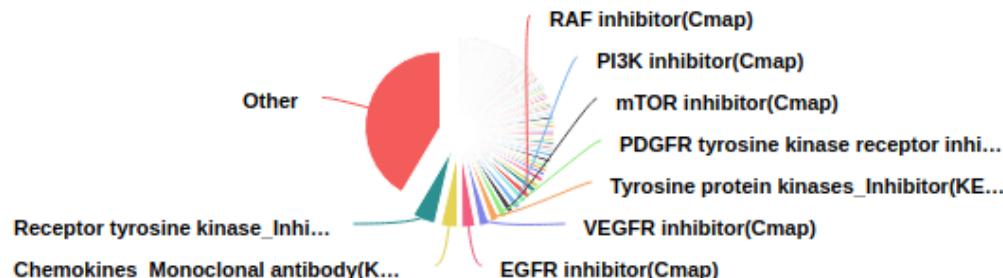
Drugs by approval status

≡



Drugs by family

≡



Target-based classification of drugs



Mechanism of Action (MOA) classification of drugs

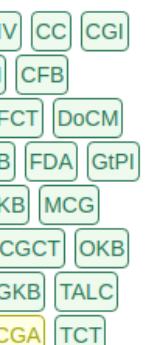
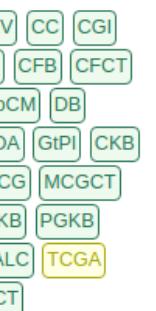
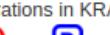


Gene search example - Table

Actions	Gene(s)	Drug	Interaction	Drug status	Type of therapy	Drug response	Family	Source(s)	DScore	GScore	BTC
	EGFR, KRAS and TP53	PANITUMU MAB		Approved for colon and rectum cancer	Targeted therapy	Both	Chemokines_Monoclonal antibody(KEGG) and Receptor tyrosine kinase_Inhibitor(KEGG)	 	0.9400	0.8648	
	EGFR, KRAS and TP53	ERLOTINIB		Approved for lung cancer	Targeted therapy	Both	EGFR inhibitor(Cmap) and Receptor tyrosine kinase_Inhibitor(KEGG)	 	0.9400	0.8648	

EGFR mutation (T790M) and EGFR amplification may induce ERLOTINIB resistance

Gene search example - Table

-	EGFR, KRAS and TP53	VEMURAFENIB		Approved for skin cancer	Targeted therapy	Both	RAF inhibitor(Cmap) and Serine/threonine protein kinases: TKL group_Inhibitor(KEGG)		0.9400	0.8648	
VEMURAFENIB is a drug approved by FDA that acts as an inhibitor of BRAF, a protein downstream to EGFR Interaction:  See pathways Alteration: mutation (V600E,V600D,V600K,V600M,V600G,V600R,V600X) Find more info for VEMURAFENIB and BRAF in: [PubMed] [ClinicalTrials.gov]		Sensitivity	RAF inhibitor(Cmap) and Serine/threonine protein kinases: TKL group_Inhibitor(KEGG)		0.9400	0.8648					
Molecular alterations in TP53 are associated with response to VEMURAFENIB, a drug approved by FDA Interaction:  Alteration: mutation (D259Y) Find more info for VEMURAFENIB and TP53 in: [PubMed] [ClinicalTrials.gov]		Sensitivity	RAF inhibitor(Cmap) and Serine/threonine protein kinases: TKL group_Inhibitor(KEGG)		0.8320	0.6384					
Molecular alterations in EGFR are associated with response to VEMURAFENIB, a drug approved by FDA Interaction:  Alteration: amplification; mutation (G465R) Find more info for VEMURAFENIB and EGFR in: [PubMed] [ClinicalTrials.gov]		Resistance	RAF inhibitor(Cmap) and Serine/threonine protein kinases: TKL group_Inhibitor(KEGG)		-0.8320	0.8648					
Molecular alterations in KRAS are associated with response to VEMURAFENIB, a drug approved by FDA Interaction:  Alteration: mutation (A146T,A146V,G12D,G13D); amplification Find more info for VEMURAFENIB and KRAS in: [PubMed] [ClinicalTrials.gov]		Resistance	RAF inhibitor(Cmap) and Serine/threonine protein kinases: TKL group_Inhibitor(KEGG)		-0.8320	0.7327					

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