IRF1 and INSR are promising druggable targets for treating Colorectal Neoplasms that control activity of RXRA, NR3C1 and RUNX1 transcription factor on promoters of genes carrying sequence variations

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Genome Enhancer release 3.6 (TRANSFAC®, TRANSPATH® and HumanPSD™ release 2025.1)

Abstract

In the present study we applied the software package "Genome Enhancer" to a data set that contains *genomics* data. The study is done in the context of *Colorectal Neoplasms*. The goal of this pipeline is to identify potential drug targets in the molecular network that governs the studied pathological process. In the first step of analysis pipeline discovers transcription factors (TFs) that regulate genes activities in the pathological state. The activities of these TFs are controlled by so-called master regulators, which are identified in the second step of analysis. After a subsequent druggability checkup, the most promising master regulators are chosen as potential drug targets for the analyzed pathology. At the end the pipeline comes up with (a) a list of known drugs and (b) investigational active chemical compounds with the potential to interact with selected drug targets.

From the data set analyzed in this study, we found the following TFs to be potentially involved in the regulation of the genes carrying sequence variations: RXRA, NR3C1 and RUNX1. The subsequent network analysis suggested

- Ubc9(h):sumo3
- PKCzeta
- IRF-1
- InsR
- Ubc9:sumo3

as the most promising molecular targets for further research, drug development and drug repurposing initiatives on the basis of identified molecular mechanism of the studied pathology.

1. Introduction

Recording "-omics" data to measure gene activities, protein expression or metabolic events is becoming a standard approach to characterize the pathological state of an affected organism or tissue. Increasingly, several of these methods are applied in a combined approach leading to large "multiomics" datasets. Still the challenge remains how to reveal the underlying molecular mechanisms that render a given pathological state different from the norm. The disease-causing mechanism can be described by a re-wiring of the cellular regulatory network, for instance as a result of a genetic or epigenetic alterations influencing the activity of relevant genes. Reconstruction of the disease-specific regulatory networks can help identify potential master regulators of the respective pathological process. Knowledge about these master regulators can point to ways how to block a pathological regulatory cascade. Suppression of certain molecular targets as components of these cascades may stop the pathological process and cure the disease.

Conventional approaches of statistical "-omics" data analysis provide only very limited information about the causes of the observed phenomena and therefore contribute little to the understanding of the pathological molecular mechanism. In contrast, the "upstream analysis" method [1-4] applied here has been deviced to provide a casual interpretation of the data obtained for a pathology state. This approach comprises two major steps: (1) analysing promoters and enhancers of genes carrying sequence variations for the transcription factors (TFs) involved in their regulation and, thus, important for the process under study; (2) re-constructing the signaling pathways that activate these TFs and identifying master regulators at the top of such pathways. For the first step, the database TRANSFAC® [5] is employed together with the TF binding site identification algorithms Match [6] and CMA [7]. The second step involves the signal transduction database TRANSPATH® [8] and special graph search algorithms [10-11] implemented in the software "Genome Enhancer".

The "upstream analysis" approach has now been extended by a third step that reveals known drugs suitable to inhibit (or activate) the identified molecular targets in the context of the disease under study. This step is performed by using information from HumanPSD™ database [11]. In addition, some known drugs and investigational active chemical compounds are subsequently predicted as potential ligands for the revealed molecular targets. They are predicted using a pre-computed database of spectra of biological activities of chemical compounds of a library of 2245 known drugs and investigational chemical compounds from HumanPSD™ database. The spectra of biological activities for these compounds are computed using the program PASS on the basis of a (Q)SAR approach [12-14]. These predictions can be used for the research purposes - for further drug development and drug repurposing initiatives.

2. Data

For this study the following experimental data was used:

Table 1. Experimental datasets used in the study

File name	Data type
CRC_variants	Genomics

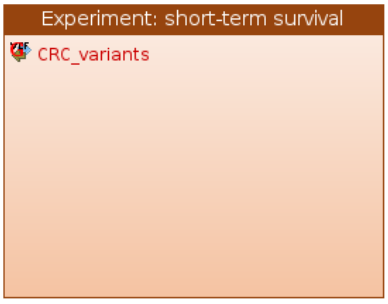


Figure 1. Annotation diagram of experimental data used in this study. With the colored boxes we show those sub-categories of the data that are compared in our analysis.

3. Results

We have analyzed the following condition: Experiment: short-term survival.

3.1. Identification of target genes

In the first step of the analysis ***target genes*** were identified from the uploaded experimental data. The most frequently mutated genes were used as target genes.

Table 2. Top ten the most frequently mutated genes in Experiment: short-term survival.
See full table →

ID	Gene description	Gene symbol	Gene schematic representation	Number of variations	Gene weight	Weighted score
ENSG00000132570	pterin-4 alpha-carbinolamine dehydratase 2	PCBD2		172	430.35	645.52
ENSG00000204525	major histocompatibility complex, class I, C	HLA-C		71	165.55	496.64
ENSG00000169894	mucin 3A, cell surface associated	MUC3A		68	160.61	481.82
ENSG00000206503	major histocompatibility complex, class I, A	HLA-A		73	158.34	475.02
ENSG00000228716	dihydrofolate reductase	DHFR		56	139.94	419.82
ENSG00000196735	major histocompatibility complex, class II, DQ alpha 1	HLA-DQA1		63	134.8	404.4
ENSG00000111700	solute carrier organic anion transporter family member 1B3	SLCO1B3		51	125.68	377.04
ENSG00000242086	MUC20 overlapping transcript	MUC20-OT1		147	341.57	341.57
ENSG00000234745	major histocompatibility complex, class I, B	HLA-B		51	111.84	335.51
ENSG00000003402	CASP8 and FADD like apoptosis regulator	CFLAR		43	110.05	330.15

3.2. Functional classification of genes

A functional analysis of genes carrying sequence variations was done by mapping the genes to several known ontologies, such as Gene Ontology (GO), disease ontology (based on HumanPSD™ database) and the ontology of signal transduction and metabolic pathways from the TRANSPATH® database. Statistical significance was computed using a binomial test.
Figures 2-4 show the most significant categories.

The most frequently mutated genes in Experiment: short-term survival:

300 top mutated genes were taken for the mapping.

GO (biological process)

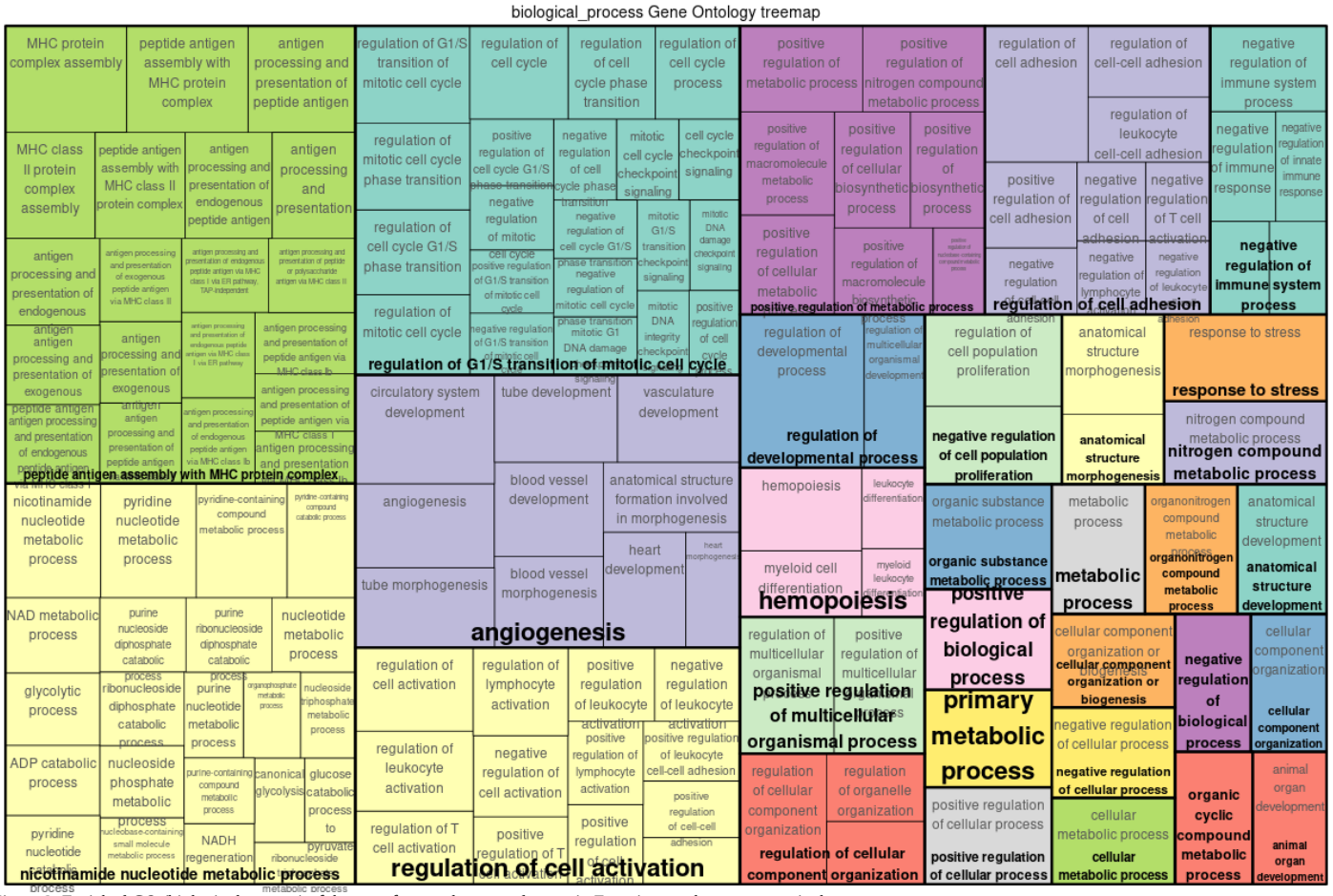


Figure 2. Enriched GO (biological process) of the most frequently mutated genes in Experiment: short-term survival.
Full classification →

TRANSPATH® Pathways (2025.1)

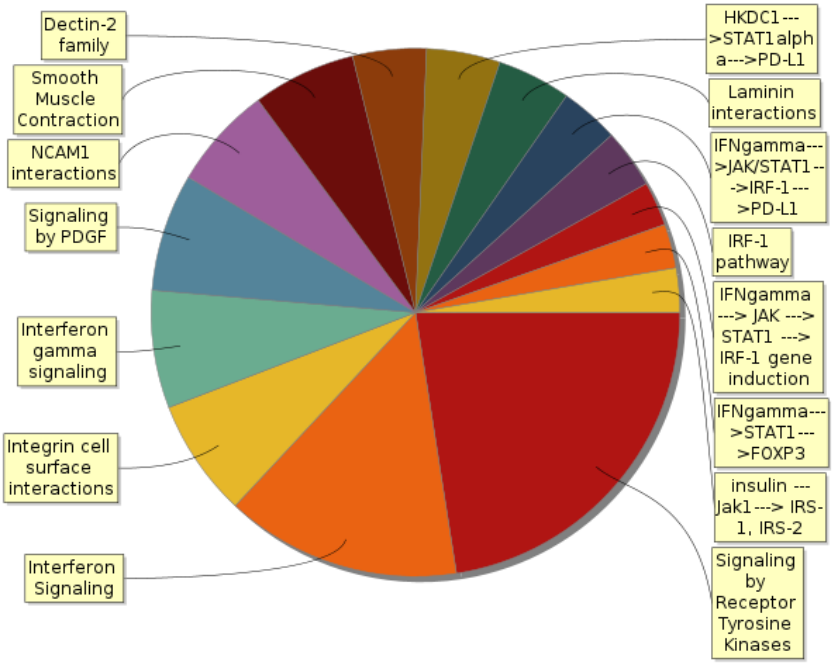


Figure 3. Enriched TRANSPATH® Pathways (2025.1) of the most frequently mutated genes in Experiment: short-term survival.
Full classification →

HumanPSD(TM) disease (2025.1)

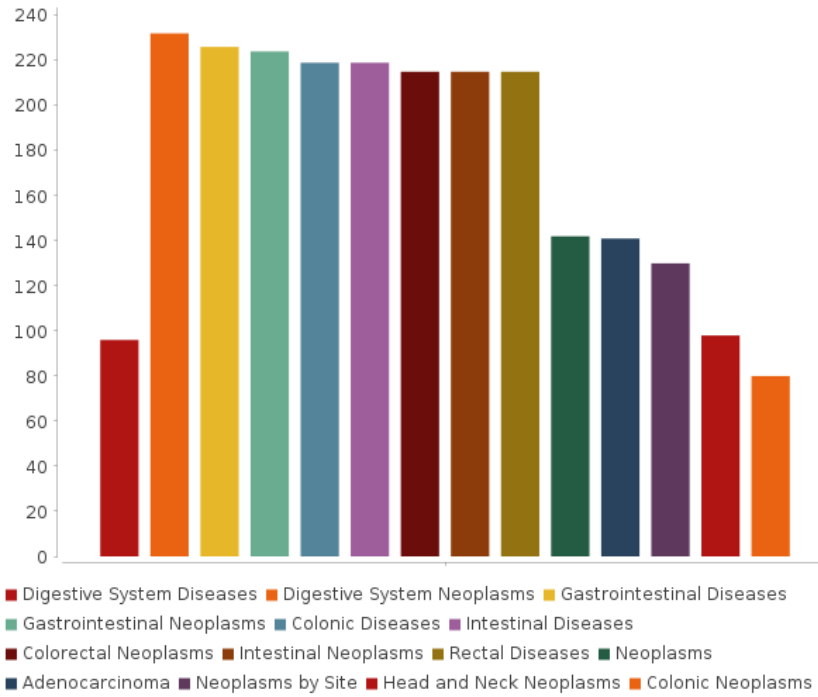
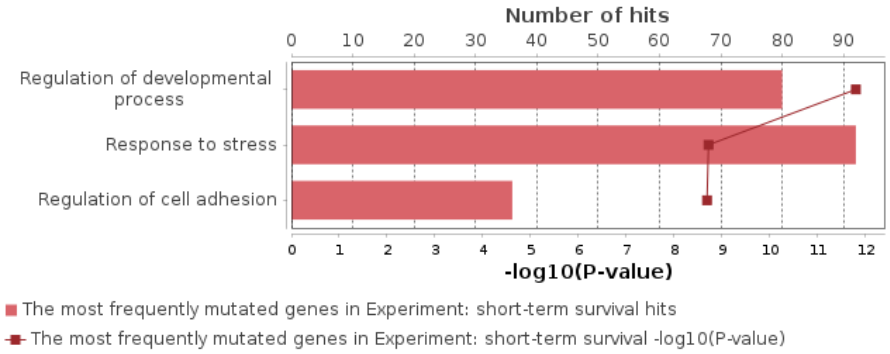


Figure 4. Enriched HumanPSD(TM) disease (2025.1) of the most frequently mutated genes in Experiment: short-term survival. The size of the bars correspond to the number of biomarkers of the given disease found among the input set.

Full classification →

The result of overall Gene Ontology (GO) analysis of the genes carrying sequence variations of the studied pathology can be summarized by the following diagram, revealing the most significant functional categories overrepresented among the observed (genes carrying sequence variations):



3.3. Analysis of enriched transcription factor binding sites and composite modules

In the next step a search for transcription factors binding sites (TFBS) was performed in the regulatory regions of the ***target genes*** by using the TF binding motif library of the TRANSFAC® database. We searched for so called **composite modules** that act as potential condition-specific **enhancers** of the ***target genes*** in their upstream regulatory regions (-1000 bp upstream of transcription start site (TSS)) and identify transcription factors regulating activity of the genes through such **enhancers**.

Classically, **enhancers** are defined as regions in the genome that increase transcription of one or several genes when inserted in either orientation at various distances upstream or downstream of the gene [7]. Enhancers typically have a length of several hundreds of nucleotides and are bound by multiple transcription factors in a cooperative manner [8].

In the current work, we use the Genomics data from the "Yes VCF track" track to predict positions of potential ***enhancers*** where the observed sequence variations may influence the gene expression in the pathology under study. We scan 5kb flanking regions and the body of all genes caring the variations, with a sliding window of 1100bp size and find the position of the window with the maximal sum of the mutation weights, where we then perform the search for potential condition-specific enhancers (CMA model search).

We analyzed mutations that were revealed in the potential enhancers located upstream, downstream or inside the ***target genes*** (see Table 3). We identified 24718 mutations potentially affecting gene regulation. Table 4 shows the following lists of PWMs whose sites were lost or gained due to these mutations. Weighting of mutations was done in respect to the significance of the change in TF affinity binding to the sequence. Mutations that maximally affected the change of binding affinity received higher weights. These PWMs were put in focus of the CMA algorithm that constructs the model of the enhancers by specifying combinations of TF motifs (see more details of the algorithm in the Methods section).

Table 3. Mutations revealed in the most frequently mutated genes

See full table →

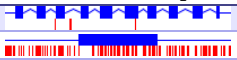
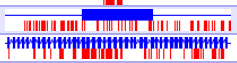
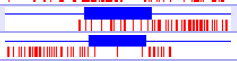
ID	Gene symbol	Gene schematic representation	Number of variations
ENSG00000132570	PCBD2		660
ENSG00000248923	MTND5P11		459
ENSG00000247627	MTND4P12		374
ENSG00000293331	ENSG00000293331		360
ENSG00000249119	MTND6P4		279
ENSG00000242086	MUC20-OT1		252
ENSG00000198868	MTND4LP30		245
ENSG00000263963	ENSG00000263963		245
ENSG00000154237	LRRK1		230
ENSG00000244921	MTCYBP18		225

Table 4. PWMs whose sites were lost or gained due to mutations in the most frequently mutated genes

See full table →

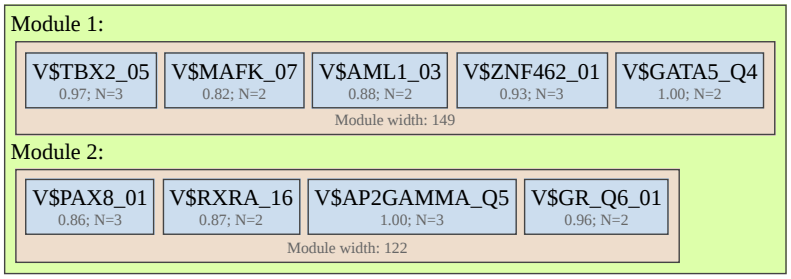
ID	P-value (gains)	P-value (losses)	yesCount (gains)	yesCount (losses)
V$OTX2_06	3.65E-2	8.72E-14	25	70
V$GSC_04	3.12E-2	3.07E-11	5	82
V$RBAK_01	3.12E-2	5.35E-10	5	381
V$ZBTB33_07	1.06E-2	8.27E-12	13	611
V$ZBTB33_05	6.47E-3	6.92E-10	12	535
V$MATH1_Q2	1.99E-3	3.66E-12	204	389
V$E2A_03	1.6E-3	1.14E-12	231	387
V$MAFG_12	3.44E-5	3.47E-10	34	1295
V$E2F8_03	1.22E-6	1.32E-9	63	1618
V$CGBP_01	8.67E-23	4.62E-12	1755	1497
V$E2F4DP1_01	1.88E-25	1.14E-10	3568	4126
V$E2F1DP2_01	2.9E-31	1.81E-11	3552	3615
V$E2F3_12	1.1E-31	3.12E-2	1493	5
V$AP2GAMMA_Q5	6.21E-33		585	
V$E2F6_05	2.91E-34	4.61E-2	771	10
V$E2F_Q4_02	1.46E-35	2.93E-2	2015	55
V$E2F1_04	2.31E-36		903	
V$GCM2SOX15_01	3.53E-39		1927	
V$E2F3_09	1.41E-41		3966	
V$TBX2_05	1.14E-41		2457	

We applied the Composite Module Analyst (CMA) [7] method to detect such potential enhancers, as targets of multiple TFs bound in a cooperative manner to the regulatory regions of the genes of interest. CMA applies a genetic algorithm to construct a generalized model of the enhancers by specifying combinations of TF motifs (from TRANSFAC®) whose sites are most frequently clustered together in the regulatory regions of the studied genes. CMA identifies the transcription factors that through their cooperation provide a synergistic effect and thus have a great influence on the gene regulation process.

Enhancer model potentially involved in regulation of target genes (the most frequently mutated genes in Experiment: short-term survival).

To build the most specific composite modules we choose top mutated genes as the input of CMA algorithm. The obtained CMA model is then applied to compute CMA score for all the most frequently mutated genes in Experiment: short-term survival.

The model consists of 2 module(s). Below, for each module the following information is shown:
- PWMs producing matches,
- number of individual matches for each PWM,
- score of the best match.



Model score (-p*log10(pval)): 22.56
Wilcoxon p-value (pval): 2.42e-44
Penalty (p): 0.517
Average yes-set score: 10.16
Average no-set score: 8.52
AUC: 0.76
Separation point: 9.29
False-positive: 32.05%
False-negative: 24.33%

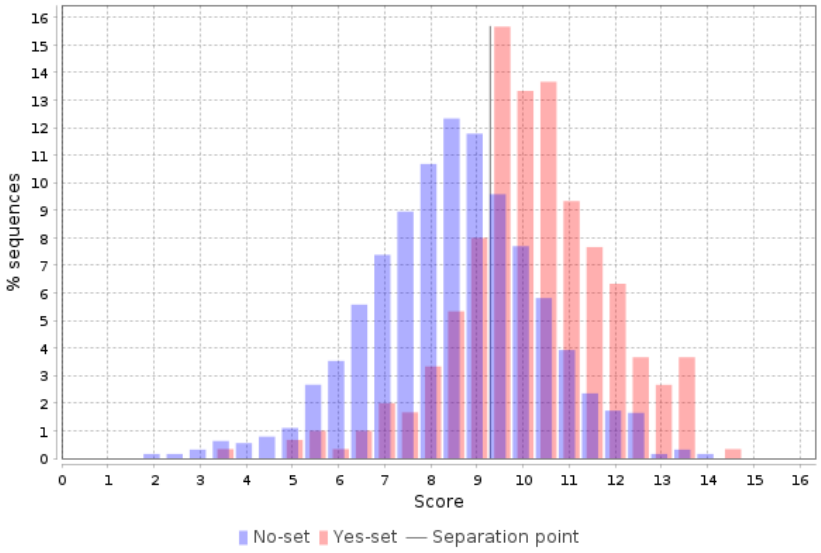


Table 5. List of top ten the most frequently mutated genes in Experiment: short-term survival with identified enhancers in their regulatory regions. ***CMA score*** *- the score of the CMA model of the enhancer identified in the regulatory region.*

See full table →

Ensembl IDs	Gene symbol	Gene description	CMA score	Factor names
ENSG00000214826	DDX12P	DEAD/H-box helicase 12, pseudogene	15.75	AP-2gamma(h), GR(h), RXRalpha(h), MafK(h), TBX2(h), ZNF462(h), Runx1(h)...
ENSG00000211656	IGLV2-33	immunoglobulin lambda variable 2-33 (non-functional)	15.44	Runx1(h), Pax-8(h), AP-2gamma(h), RXRalpha(h), GR(h), ZNF462(h), TBX2(h)...
ENSG00000290985	SLC6A10P	solute carrier family 6 member 10, pseudogene	15.36	Runx1(h), Pax-8(h), TBX2(h), MafK(h), ZNF462(h), GR(h), AP-2gamma(h)...
ENSG00000214614		novel transcript	15.36	Runx1(h), Pax-8(h), TBX2(h), MafK(h), ZNF462(h), GR(h), AP-2gamma(h)...
ENSG00000214617	SLC6A10P	solute carrier family 6 member 10, pseudogene	15.36	Runx1(h), Pax-8(h), TBX2(h), MafK(h), ZNF462(h), GR(h), AP-2gamma(h)...
ENSG00000070610	GBA2	glucosylceramidase beta 2	15.27	TBX2(h), GATA-5(h), Runx1(h), ZNF462(h), MafK(h), Pax-8(h), RXRalpha(h)...
ENSG00000117877	POLR1G	RNA polymerase I subunit G	15.18	ZNF462(h), GATA-5(h), Runx1(h), MafK(h), TBX2(h), GR(h), AP-2gamma(h)...
ENSG00000065802	ASB1	ankyrin repeat and SOCS box containing 1	15.12	Runx1(h), MafK(h), TBX2(h), Pax-8(h), ZNF462(h), GATA-5(h), RXRalpha(h)...
ENSG00000267280	TBX2-AS1	TBX2 antisense RNA 1	15.11	ZNF462(h), TBX2(h), GATA-5(h), Pax-8(h), RXRalpha(h), GR(h), AP-2gamma(h)...
ENSG00000121068	TBX2	T-box transcription factor 2	15.11	ZNF462(h), TBX2(h), GATA-5(h), Pax-8(h), RXRalpha(h), GR(h), AP-2gamma(h)...

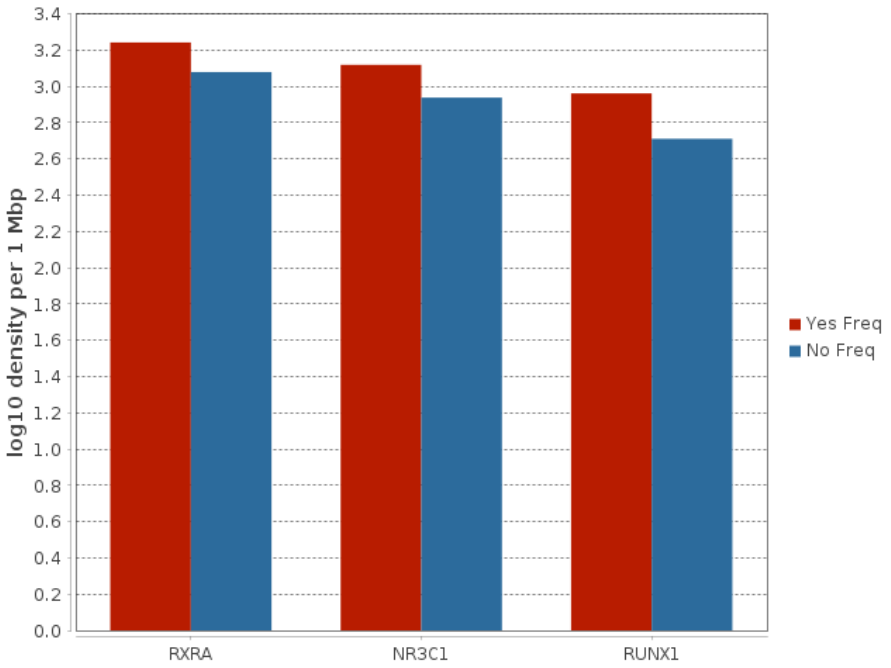
On the basis of the enhancer models we identified transcription factors potentially regulating the ***target genes*** of our interest. We found 9 transcription factors controlling expression of the genes associated with genomic variations (see Table 6).

Table 6. Transcription factors of the predicted enhancer model potentially regulating the genes carrying sequence variations (the most frequently mutated genes in Experiment: short-term survival). ***Yes-No ratio*** *is the ratio between frequencies of the sites in Yes sequences versus No sequences. It describes the level of the enrichment of binding sites for the indicated TF in the regulatory target regions.* ***Regulatory score*** *is the measure of involvement of the given TF in the controlling of expression of genes that encode master regulators presented below (through positive feedback loops).*

See full table →

ID	Gene symbol	Gene description	Regulatory score	Yes-No ratio
MO000019619	RXRA	retinoid X receptor alpha	7.57	1.46
MO000031266	NR3C1	nuclear receptor subfamily 3 group C member 1	6.84	1.52
MO000025375	RUNX1	RUNX family transcription factor 1	5.96	1.78
MO000028668	MAFK	MAF bZIP transcription factor K	5.91	3.46
MO000026866	PAX8	paired box 8	4.95	1.3
MO000028209	TBX2	T-box transcription factor 2	4.73	5.93
MO000092587	ZNF462	zinc finger protein 462	4.39	1.15
MO000026664	GATA5	GATA binding protein 5	2.51	1.24
MO000026449	TFAP2C	transcription factor AP-2 gamma	0	2.3

The following diagram represents the key transcription factors, which were predicted to be potentially regulating genes carrying sequence variations in the analyzed pathology: RXRA, NR3C1 and RUNX1.



3.4. Finding master regulators in networks

In the second step of the upstream analysis common regulators of the revealed TFs were identified. We identified 172 signaling proteins whose structure and function is highly damaged by the mutations (see Table 7).

Table 7. Signaling proteins whose structure and function are damaged by the mutations in the most frequently mutated genes

See full table →

ID	Title	Mutation count	Consequence	Codons
MO000019673	p85alpha(h)	22	stop_gained	Cga/Tga
MO000138949	Drp1(h)	22	NMD_transcript_variant,stop_gained	Gaa/Taa
MO000206935	C11orf74(h)	12	stop_gained	Gaa/Taa
MO000167580	Sur-8(h)	11	NMD_transcript_variant,stop_gained	Gaa/Taa
MO000168719	GIPN(h)	10	NMD_transcript_variant,frameshift_variant	aat/aaAt
MO000211774	DPAGT1(h)	10	NMD_transcript_variant,frameshift_variant	ttc/ttTc
MO000190658	GPSM2(h)	9	stop_gained	Gaa/Taa
MO000093071	chd8(h)	8	stop_gained	taC/taA
MO000113258	MYPT1(h)	8	NMD_transcript_variant,frameshift_variant	aga/aAga
MO000127741	SMC4L1(h)	8	stop_gained	Cga/Tga

Top 100 mutated proteins for the most frequently mutated genes were used in the algorithm of master regulator search as a list of nodes of the signal transduction network that are removed from the network during the search of master regulators (see more details about the algorithm in the Methods section). These master regulators appear to be the key candidates for therapeutic targets as they have a master effect on regulation of intracellular pathways that activate the pathological process of our study. The identified master regulators are shown in Table 8.

Table 8. Master regulators that may govern the regulation of the most frequently mutated genes in Experiment: short-term survival. ***Total rank*** *is the sum of the ranks of the master molecules sorted by keynode score, CMA score, genomics data.*
See full table →

ID	Master molecule name	Gene symbol	Gene description	Total rank	Weighted score
MO001080010	Ubc9(h){sumo3C93}:sumo3(h){clCG92,93}	SUMO3, UBE2I	small ubiquitin like modifier 3, ubiquitin conjugating enzyme E2 I	192	183.78
MO001088545	Ubc9{sumo3C93}:sumo3{clCG92,93}	SUMO3, UBE2I	small ubiquitin like modifier 3, ubiquitin conjugating enzyme E2 I	214	183.78
MO000019975	Ubc9(h)	UBE2I	ubiquitin conjugating enzyme E2 I	367	183.78
MO001079984	Ubc9(h){sumoC93}:sumo1(h){clCG97,93}	SUMO1, UBE2I	small ubiquitin like modifier 1, ubiquitin conjugating enzyme E2 I	368	183.78
MO000079234	Ubc9(h)	UBE2I	ubiquitin conjugating enzyme E2 I	370	183.78
MO001088543	Ubc9{sumoC93}:sumo1{clCG97,93}	SUMO1, UBE2I	small ubiquitin like modifier 1, ubiquitin conjugating enzyme E2 I	373	183.78
MO001080002	Ubc9(h){sumo2C93}:SUMO2(h) {clCG93,93}	SUMO2, UBE2I	small ubiquitin like modifier 2, ubiquitin conjugating enzyme E2 I	374	183.78
MO001088544	Ubc9{sumo2C93}:SUMO2{clCG93,93}	SUMO2, UBE2I	small ubiquitin like modifier 2, ubiquitin conjugating enzyme E2 I	394	183.78
MO000007686	IRF-1(h)	IRF1	interferon regulatory factor 1	402	216.55
MO000031039	NCoR2(h)	NCOR2	nuclear receptor corepressor 2	439	191.29

The intracellular regulatory pathways controlled by the above-mentioned master regulators are depicted in Figure 5. This diagram displays the connections between identified transcription factors, which play important roles in the regulation of genes carrying sequence variations, and selected master regulators, which are responsible for the regulation of these TFs.

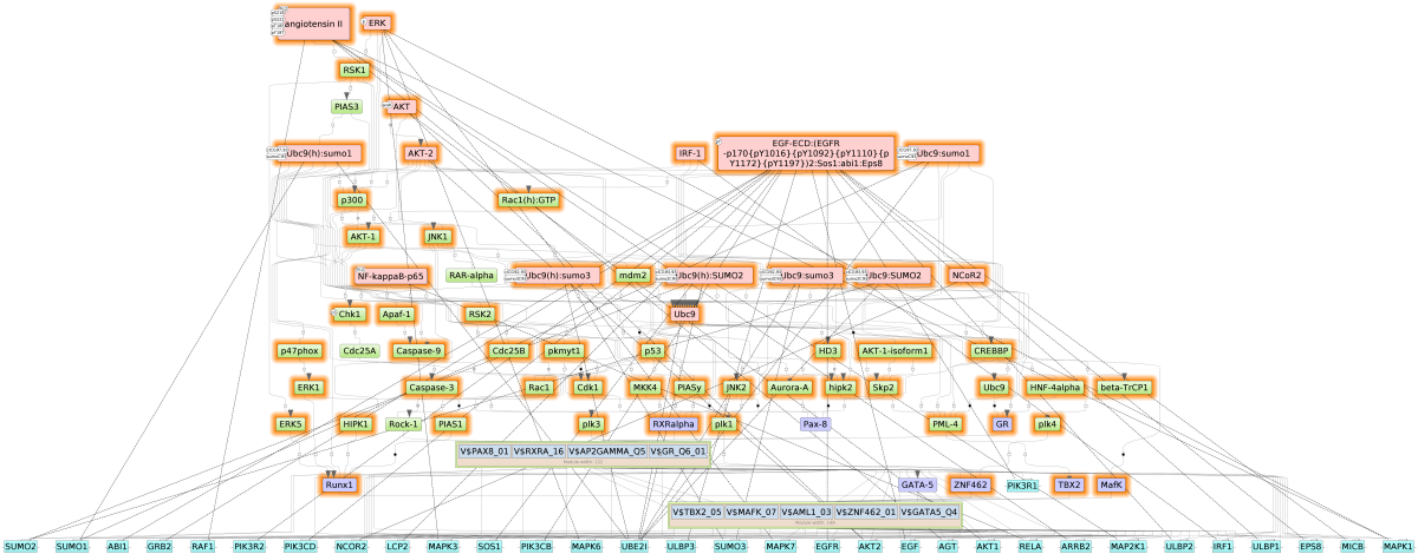


Figure 5. Diagram of intracellular regulatory signal transduction pathways of the most frequently mutated genes in Experiment: short-term survival. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate molecules, which have been added to the network during the search for master regulators from selected TFs. Orange frames highlight molecules presented in original mapping.
See full diagram →

4. Finding prospective drug targets

The identified master regulators that may govern pathology associated genes were checked for druggability potential using HumanPSD™ [11] database of gene-disease-drug assignments and PASS [12-14] software for prediction of biological activities of chemical compounds on the basis of a (Q)SAR approach. Respectively, for each master regulator protein we have computed two Druggability scores: HumanPSD Druggability score and PASS Druggability score. Where Druggability score represents the number of drugs that are potentially suitable for inhibition (or activation) of the corresponding target either according to the information extracted from medical literature (from HumanPSD™ database) or according to cheminformatics predictions of compounds activity against the examined target (from PASS software).

The cheminformatics druggability check is done using a pre-computed database of spectra of biological activities of chemical compounds from a library of all small molecular drugs from HumanPSD™ database, 2507 pharmaceutically active known chemical compounds in total. The spectra of biological activities has been computed using the program PASS [12-14] on the basis of a (Q)SAR approach.

If both Druggability scores were below defined thresholds (see Methods section for the details) such master regulator proteins were not used in further analysis of drug prediction.

As a result we created the following two tables of prospective drug targets (top targets are shown here):

*Table 9. Prospective drug targets selected from full list of identified master regulators filtered by Druggability score from HumanPSD™ database. **Druggability score** contains the number of drugs that are potentially suitable for inhibition (or activation) of the target. The drug targets are sorted according to the **Total rank** which is the sum of three ranks computed on the basis of the three scores: keynode score, CMA score and expression change score (logFC, if present). See Methods section for details.*

See full table →

Gene symbol	Gene Description	Druggability score	Total rank	Weighted score
IRF1	interferon regulatory factor 1	1	240	216.55
INSR	insulin receptor	52	268	104.22
PML	PML nuclear body scaffold	1	323	138.3
PRKCZ	protein kinase C zeta	17	342	90.11
RPS6KA1	ribosomal protein S6 kinase A1	37	357	74.63
HIF1A	hypoxia inducible factor 1 subunit alpha	22	429	103.37

*Table 10. Prospective drug targets selected from full list of identified master regulators filtered by Druggability score predicted by PASS software. Here, the **Druggability score** for master regulator proteins is computed as a sum of PASS calculated probabilities to be active as a target for various small molecular compounds. The drug targets are sorted according to the **Total rank** which is the sum of three ranks computed on the basis of the three scores: keynode score, CMA score and expression change score (logFC, if present). See Methods section for details.*

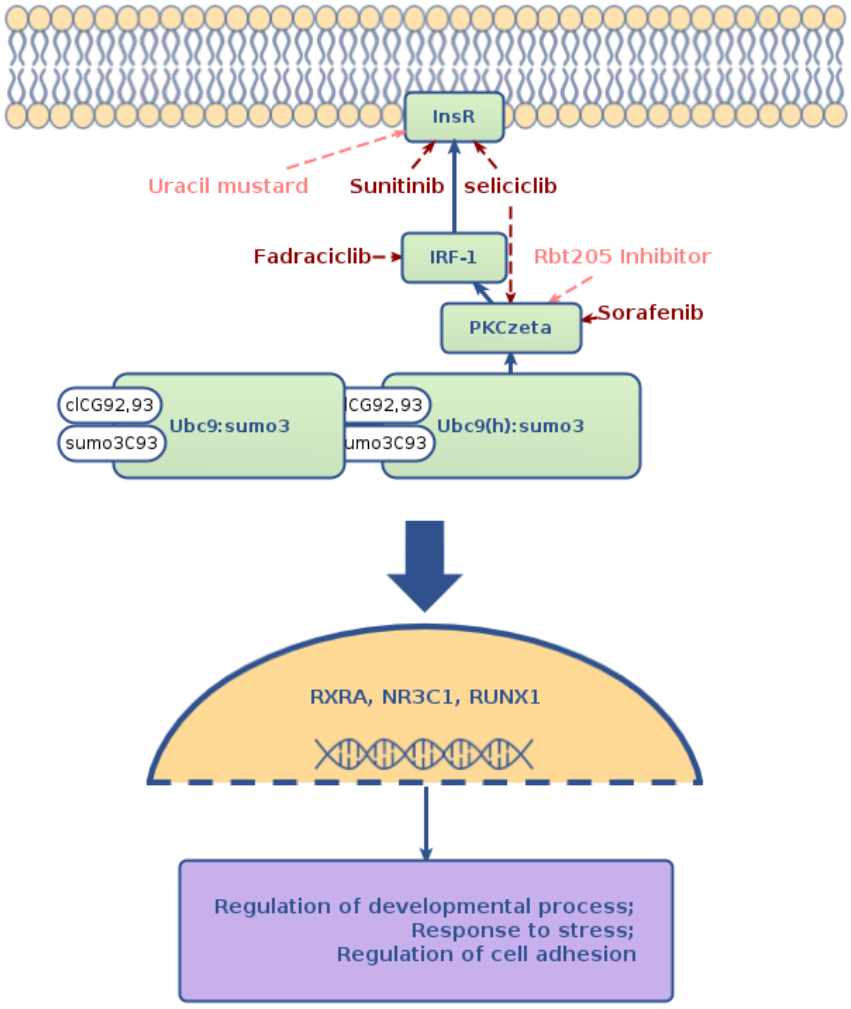
See full table →

Gene symbol	Gene Description	Druggability score	Total rank	Weighted score
INSR	insulin receptor	3.03	268	104.22
PRKCZ	protein kinase C zeta	18.14	342	90.11
RPS6KA1	ribosomal protein S6 kinase A1	4.17	357	74.63
HIF1A	hypoxia inducible factor 1 subunit alpha	43.84	429	103.37
PCBD2	pterin-4 alpha-carbinolamine dehydratase 2	0.35	462	645.52
MAP2K7	mitogen-activated protein kinase kinase 7	0.39	500	69.08

Below we represent schematically the main mechanism of the studied pathology. In the schema we considered the top two drug targets of each of the two categories computed above. In addition we have added two top identified master regulators for which no drugs may be identified yet, but that are playing the crucial role in the molecular mechanism of the studied pathology. Thus the molecular mechanism of the studied pathology was predicted to be mainly based on the following key master regulators:

- Ubc9(h):sumo3
- PKCzeta
- IRF-1
- InsR
- Ubc9:sumo3

This result allows us to suggest the following schema of affecting the molecular mechanism of the studied pathology:



Drugs which are shown on this schema: Fadraciclib, Sunitinib, Sorafenib, Uracil mustard, seliciclib and Rbt205 Inhibitor, should be considered as a prospective research initiative for further drug repurposing and drug development. These drugs were selected as top matching treatments to the most prospective drug targets of the studied pathology, however, these results should be considered with special caution and are to be used for research purposes only, as there is not enough clinical information for adapting these results towards immediate treatment of patients.

The drugs given in dark red color on the schema are FDA approved drugs or drugs which have gone through various phases of clinical trials as active treatments against the selected targets.
The drugs given in pink color on the schema are drugs, which were cheminformatically predicted to be active against the selected targets.

5. Identification of potential drugs

In the last step of the analysis we strived to identify known activities as well as drugs with cheminformatically predicted activities that are potentially suitable for inhibition (or activation) of the identified molecular targets in the context of specified human diseases(s).

Proposed drugs are top ranked drug candidates, that were found to be active on the identified targets and were selected from 4 categories:

1. FDA approved drugs or used in clinical trials drugs for the studied pathology;
2. Repurposing drugs used in clinical trials for other pathologies;
3. Drugs, predicted by PASS to be active against identified drug targets and against the studied pathology;
4. Drugs, predicted by PASS to be active against identified drug targets but for other pathologies.

Proposed drugs were selected on the basis of Drug rank which was computed from the ranks sum based on the individual ranks of the following scores:

- Target activity score (depends on ranks of all targets that were found for the selected drug);
- Disease activity score (weighted sum of number of clinical trials on disease(s) under study where the selected drug is known to be applied or PASS Disease activity score - cheminformatically predicted property of the compound to be active against the studied disease(s));
- Clinical validity score (applicable only for drugs predicted on the basis of literature curation in HumanPSD™ database (Tables 12 and 13), reflects the number of the highest clinical trials phase on which the drug was tested for any pathology).

You can refer to the Methods section for more details on drug ranking procedure.

Based on the Drug rank, a numerical value of Drug score was calculated, which reflects the potential activity of the respective drug on the overall molecular mechanism of the studied pathology. Drug score values belong to the range from 1 to 100 and are calculated as a quotient of maximum drug rank and the drug rank of the given drug multiplied by 100.

If sufficient information regarding the known associations between predicted drugs and variants identified in the studied pathology was found, this will be reflected in the ***Somatic variants*** column of the FDA approved and repurposed drugs used in clinical trials tables. Details on these variant-drug associations can be found in the Molecular Tumor Board (MTB) report generated for the studied pathology.

Top drugs of each category are given in the tables below:

Drugs approved in clinical trials for Oncology

Table 11. Clinically approved (FDA, ENA, etc.) drugs for the studied pathology (most promising and clinically approved treatment candidates selected for the identified drug targets on the basis of literature curation in HumanPSD™ database)

See full table →

Name	Target names	Drug score	Disease activity score	Disease trial phase	Approved
Regorafenib	KIT, MAPK1, ABL1, KDR, FGFR2, PDGFRB, FGFR1, BRAF, PDGFRA, RAF1, FLT4, FRS2, MAPK11, EPHA2, FLT1, AKT1, DDR2, TEK, MAPK3, RET, AKT2	96	6	Phase 3: Colorectal Neoplasms, Carcinoma, Carcinoma, Hepatocellular, Gastrointestinal Stromal Tumors, Glioblastoma, Neoplasm Metastasis, Neoplasms, Rectal Neoplasms	Colorectal Neoplasms (FDA)
Oxaliplatin	CTNNB1, IGF2, MMP9, CDH1, AKT1, AKT2	86	12	Phase 4: Colorectal Neoplasms, Colonic Neoplasms, Digestive System Neoplasms, Gastrointestinal Neoplasms, Intestinal Neoplasms, Liver Neoplasms, Neoplasm Metastasis, Neoplasms, Postoperative Complications, Rectal Neoplasms	Colorectal Neoplasms (FDA, PUBMED)
encorafenib	MAPK10, MAPK1, MAPK8, MAPK9, MAPK7, MAPK6, LIMK1, BRAF, MAPK3, MAP2K4, RAF1	86	5	Phase 3: Colorectal Neoplasms, Biliary Tract Neoplasms, Melanoma, Neoplasms, Rectal Neoplasms	Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, FDA)
Fluorouracil	IL6R, ERCC1, CASP8, CASP3, BAX, FAS, BIRC5, CDKN1A	82	11	Phase 4: Colorectal Neoplasms, Bowen's Disease, Breast Neoplasms, Carcinoma, Carcinoma, Basal Cell, Carcinoma, Squamous Cell, Digestive System Neoplasms, Gastrointestinal Neoplasms, Glaucoma, Head and Neck Neoplasms, Hypopigmentation, Intestinal Neoplasms, Keratosis, Keratosis, Actinic, Neoplasms, Neoplasms, Basal Cell, Neoplasms, Squamous Cell, Photosensitivity Disorders, Postoperative Complications, Skin Diseases, Skin Neoplasms, Squamous Cell Carcinoma of Head and Neck, Vitiligo	Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials)
fruquintinib	KDR, FLT1, FLT4	80	2	Phase 2: Colorectal Neoplasms, Adenocarcinoma, Carcinoma, Squamous Cell, Esophageal Neoplasms, Esophageal Squamous Cell Carcinoma, Neoplasms, Rectal Neoplasms, Stomach Neoplasms	Colorectal Neoplasms (FDA)
Irinotecan	MAPK10, BIRC5, TOP1, RUNX3, CDKN1A	75	12	Phase 4: Colorectal Neoplasms, Carcinoma, Neuroendocrine, Neoplasms, Neuroblastoma, Neuroendocrine Tumors, Rectal Neoplasms	Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, FDA, FDA)
Bevacizumab	FCGR2A, VEGFA, FCGR2B	65	12	Phase 4: Colorectal Neoplasms, Carcinoma, Ovarian Epithelial, Cataract, Diabetic Retinopathy, Dilatation, Pathologic, Edema, Epistaxis, Fallopian Tube Neoplasms, Glaucoma, Hemorrhage, Macular Edema, Neoplasm Metastasis, Neoplasms, Optic Nerve Diseases, Ovarian Neoplasms, Peritoneal Neoplasms, Pterygium, Rectal Neoplasms, Retinal Detachment, Retinal Diseases, Telangiectasia, Hereditary Hemorrhagic, Telangiectasis, Vitreous Hemorrhage	Colorectal Neoplasms (FDA, FDA)
Aflibercept	VEGFA, PGF	61	4	Phase 2: Colorectal Neoplasms, Astrocytoma, Brain Neoplasms, Carcinoid Tumor, Carcinoma, Carcinoma, Merkel Cell, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Cataract, Central Serous Chorioretinopathy, Diabetic Retinopathy, Edema, Esophageal Squamous Cell Carcinoma, Eye Diseases, Glioblastoma, Hemorrhage, Leukemia, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Lung Neoplasms, Macular Degeneration, Macular Edema, Neoplasm Metastasis, Neoplasms, Pseudoxanthoma Elasticum, Pterygium, Rectal Neoplasms, Retinal Degeneration, Retinal Diseases, Retinal Vein Occlusion, Retinitis, Retinitis Pigmentosa, Small Cell Lung Carcinoma, Squamous Cell Carcinoma of Head and Neck, Vitreous Hemorrhage, Wet Macular Degeneration, Xanthomatosis	Colorectal Neoplasms (FDA)
Cetuximab	FCGR2A, EGFR, FCGR2B	48	11	Phase 4: Colorectal Neoplasms, Carcinoma, Carcinoma, Squamous Cell, Head and Neck Neoplasms, Liver Neoplasms, Neoplasm Metastasis, Neoplasms, Rectal Neoplasms, Squamous Cell Carcinoma of Head and Neck	Colorectal Neoplasms (FDA, FDA)
Panitumumab	EGFR	39	5	Phase 3: Colorectal Neoplasms, Neoplasms, Rectal Neoplasms	Colorectal Neoplasms (FDA)
Capecitabine	CDKN2A	21	12	Phase 4: Colorectal Neoplasms, Neoplasms, Rectal Neoplasms	Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, FDA, FDA)

The ***Disease trial phase*** column reflects the maximum clinical trials phase in which the drug was studied for the analyzed pathology.

Drugs approved in clinical trials

Table 12. Drugs used in clinical trials for the studied pathology (most promising treatment candidates selected for the identified drug targets on the basis of literature curation in HumanPSD™ database)

See full table →

Name	Target names	Drug score	Disease activity score	Disease trial phase
Sunitinib	BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, CAMK1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, HUNK, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, SIRT3, PRKCA, CSNK1E, SIRT2, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, CAMKK1, EPHB1, SIRT1, TGFBR2, FYN, PRKD2, RPS6KA4	97	3	Phase 2: Colorectal Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Adrenal Cortex Neoplasms, Adrenocortical Carcinoma, Ascites, Astrocytoma, Barrett Esophagus, Blast Crisis, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Transitional Cell, Central Nervous System Neoplasms, Colonic Neoplasms, Endocrine Gland Neoplasms, Endometrial Neoplasms, Esophageal Neoplasms, Fibroma, Fibromatosis, Aggressive, Fibrosarcoma, Gastrointestinal Stromal Tumors, Glioblastoma, Glioma, Gliosarcoma, Hemangioblastoma, Hemangiopericytoma, Histiocytoma, Histiocytoma, Benign Fibrous, Histiocytoma, Malignant Fibrous, Intestinal Neoplasms, Kidney Neoplasms, Leiomyosarcoma, Leukemia, Leukemia, Hairy Cell, Leukemia, Large Granular Lymphocytic, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, Leukemia, Mast-Cell, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Accelerated Phase, Leukemia, Myeloid, Acute, Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative, Leukemia, Myeloid, Chronic-Phase, Leukemia, Myelomonocytic, Acute, Leukemia, Myelomonocytic, Chronic, Leukemia, Myelomonocytic, Juvenile, Leukemia, Prolymphocytic, Liposarcoma, Liver Neoplasms, Lung Neoplasms, Lymphoma, Lymphoma, Non-Hodgkin, Melanoma, Meningioma, Multiple Myeloma, Myelodysplastic Syndromes, Myosarcoma, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasms, Neoplasms, Germ Cell and Embryonal, Neoplasms, Hormone-Dependent, Neoplasms, Plasma Cell, Nervous System Neoplasms, Neuroendocrine Tumors, Neurofibroma, Neurofibromatoses, Neurofibromatosis 1, Ovarian Neoplasms, Pancreatic Neoplasms, Paraganglioma, Pheochromocytoma, Pica, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Preleukemia, Primary Myelofibrosis, Prostatic Neoplasms, Ranula, Rectal Neoplasms, Recurrence, Sarcoma, Sarcoma, Alveolar Soft Part, Skin Neoplasms, Small Cell Lung Carcinoma, Solitary Fibrous Tumors, Stomach Neoplasms, Syndrome, Teratoma, Testicular Neoplasms, Thymoma, Thymus Neoplasms, Thyroid Diseases, Thyroid Neoplasms, Urinary Bladder Neoplasms, Uterine Neoplasms, von Hippel-Lindau Disease
Vatalanib	BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, CAMK1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1,	97	3	Phase 3: Colorectal Neoplasms, Colonic Neoplasms, Neoplasms, Rectal Neoplasms

	MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, CDK1, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, CAMKK1, EPHB1, HLA-A, TGFBR2, FYN, PRKD2, RPS6KA4			
Sorafenib	BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, CAMK1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, HUNK, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, DYRK1A, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, RIPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, EEF2K, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFBR2, FYN, PRKD2, RPS6KA4	96	2	Phase 2: Colorectal Neoplasms, Adenocarcinoma, Adenoma, Adenoma, Liver Cell, Adrenal Cortex Neoplasms, Adrenocortical Carcinoma, Bile Duct Neoplasms, Biliary Tract Neoplasms, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Carcinoid Tumor, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Islet Cell, Carcinoma, Medullary, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Carcinoma, Transitional Cell, Cholangiocarcinoma, Desmoplastic Small Round Cell Tumor, Digestive System Neoplasms, Endocrine Gland Neoplasms, Fibrosarcoma, Gallbladder Neoplasms, Gastrinoma, Gastrointestinal Neoplasms, Gastrointestinal Stromal Tumors, Glioblastoma, Glioma, Gliosarcoma, Glucagonoma, Head and Neck Neoplasms, Hemangiosarcoma, Hepatitis, Hepatitis A, Hepatitis B, Hepatitis C, Hepatopulmonary Syndrome, Insulinoma, Intestinal Neoplasms, Kidney Diseases, Kidney Neoplasms, Leiomyosarcoma, Leukemia, Leukemia, Monocytic, Acute, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myelomonocytic, Chronic, Liver Diseases, Liver Neoplasms, Lung Neoplasms, Lymphoma, Malignant Carcinoid Syndrome, Melanoma, Mesothelioma, Mesothelioma, Malignant, Multiple Endocrine Neoplasia, Multiple Endocrine Neoplasia Type 2a, Multiple Endocrine Neoplasia Type 2b, Multiple Myeloma, Myelodysplastic Syndromes, Myeloproliferative Disorders, Myosarcoma, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasms, Neoplasms by Histologic Type, Neoplasms by Site, Neoplasms, Glandular and Epithelial, Neoplasms, Plasma Cell, Nerve Sheath Neoplasms, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroectodermal Tumors, Primitive, Peripheral, Neuroendocrine Tumors, Neurofibrosarcoma, Osteosarcoma, Ovarian Neoplasms, Pancreatic Neoplasms, Pharyngeal Neoplasms, Plasmacytoma, Preleukemia, Rectal Neoplasms, Recurrence, Rhabdomyosarcoma, Sarcoma, Sarcoma, Ewing, Sarcoma, Synovial, Somatostatinoma, Syndrome, Thyroid Diseases, Thyroid Neoplasms, Urinary Bladder Neoplasms, Vaccinia, Vipoma
Sirolimus	ROCK2, MARK3, NEK7, PRKACA, GSK3B, NEK2, NFE2L2, SGK1, CAMK1, NEK6, BAX, RPS6KA5, CSK, MAPKAPK5, PRKD1, MAPK3, MELK, MAPK8, CAMKK2, DYRK1A, MAP2K1, FGF2, PRKCZ, MAPK12, MAPK11, MAPKAPK2, CHEK2, AKT2, STK3, PDPK1, IKBKB, MAPK10, RPS6KA3, PRKCA, IL10, PRKAA1, AURKB, RPS6KA1, HSP90AA1, MAPK14, CSNK1D, PLK1, PGR, FKBP1A, EEF2K, AKT1, CHEK1, RBL2, TP53, RPS6KB1, MAPK1, HIPK2, PIM2, MAPK9, MTOR, PAK4, PIM3, MAPK13, CAMKK1, CTLA4	96	3	Phase 2: Colorectal Neoplasms, Acanthosis Nigricans, Acute Disease, Adenocarcinoma, Adenocarcinoma, Mucinous, Adenoma, Adenoma, Islet Cell, Adenomatous Polyposis Coli, Adenomatous Polyps, Alzheimer Disease, Amyotrophic Lateral Sclerosis, Anemia, Anemia, Aplastic, Anemia, Hemolytic, Anemia, Hemolytic, Autoimmune, Anemia, Refractory, Anemia, Refractory, with Excess of Blasts, Anemia, Sickle Cell, Angina Pectoris, Angina, Unstable, Angiofibroma, Angiomyolipoma, Angiomyoma, Aphasia, Aphasia, Primary Progressive, Arteriovenous Malformations, Atrophy, Autoimmune Lymphoproliferative Syndrome, Blast Crisis, Bone Marrow Failure Disorders, Brain Abscess, Brain Stem Infarctions, Breast Neoplasms, Bronchiolitis, Bronchiolitis Obliterans, Bronchiolitis Obliterans Syndrome, Burkitt Lymphoma, COVID-19, Carcinoma, Carcinoma, Endometrioid, Carcinoma, Hepatocellular, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Carcinoma, Squamous Cell, Cerebral Hemorrhage, Cerebral Intraventricular Hemorrhage, Chordoma, Cockayne Syndrome, Cognitive Dysfunction, Congenital Abnormalities, Coronary Artery Disease, Coronary Disease, Cysts, Cytopenia, Dementia, Depression, Depressive Disorder, Diabetes Mellitus, Diabetes Mellitus, Type 1, Diabetic Retinopathy, Dilatation, Pathologic, Edema, Endometrial Neoplasms, Epidermolysis Bullosa, Epidermolysis Bullosa Simplex, Epilepsy, Epistaxis, Erythema, Esophageal Squamous Cell Carcinoma, Eye Diseases, Fanconi Anemia, Fanconi Syndrome, Fibroma, Fibrosarcoma, Fibrosis, Frontotemporal Dementia, Ganglion Cysts, Ganglioneuroblastoma, Genital Diseases, Genital Diseases, Female, Geographic Atrophy, Giant Lymph Node Hyperplasia, Glioblastoma, Glioma, Gliosarcoma, Glomerulonephritis, Glomerulonephritis, IGA, Gout, Graft vs Host Disease, Graves Ophthalmopathy, Hamartoma, Hamartoma Syndrome, Multiple, Head and Neck Neoplasms, Hemangioendothelioma, Hemangioma, Hemangiosarcoma, Hematologic Diseases, Hematologic Neoplasms, Hemoglobinopathies, Hemolysis, Hemorrhage, Hodgkin Disease, Hydrocephalus, Hydrocephalus, Normal Pressure, Hyperinsulinism, Hypertension, Hyperuricemia, Hypoglycemia, Immunologic Deficiency Syndromes, Infarction, Inflammatory Bowel Diseases, Intestinal Neoplasms, Intracranial Arteriovenous Malformations, Ischemia, Kasabach-Merritt Syndrome, Kidney Diseases, Kidney Diseases, Cystic, Kidney Failure, Chronic, Klippel-Trenaunay-Weber Syndrome, Leiomyoma, Leiomyomatosis, Leiomyosarcoma, Leukemia, Leukemia, Biphenotypic, Acute, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid,

				Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Accelerated Phase, Leukemia, Myeloid, Acute, Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative, Leukemia, Myeloid, Chronic-Phase, Leukemia, Myelomonocytic, Chronic, Leukemia, Myelomonocytic, Juvenile, Leukemia, Plasma Cell, Leukemia, Prolymphocytic, Leukemia, Prolymphocytic, T-Cell, Leukemia, Promyelocytic, Acute, Lipoma, Liposarcoma, Liver Neoplasms, Lung Neoplasms, Lupus Erythematosus, Systemic, Lupus Nephritis, Lymphangioleiomyomatosis, Lymphangioma, Lymphangiomyoma, Lymphatic Abnormalities, Lymphedema, Lymphoma, Lymphoma, B-Cell, Lymphoma, B-Cell, Marginal Zone, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Large-Cell, Immunoblastic, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoproliferative Disorders, Macular Degeneration, Macular Edema, Melanoma, Metabolic Diseases, Motor Neuron Disease, Mouth Neoplasms, Multiple Myeloma, Multiple System Atrophy, Myelodysplastic Syndromes, Myelodysplastic-Myeloproliferative Diseases, Myeloproliferative Disorders, Myocardial Infarction, Myocardial Ischemia, Myoma, Myosarcoma, Myxoma, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasm Metastasis, Neoplasm, Residual, Neoplasms, Neoplasms, Plasma Cell, Neoplasms, Second Primary, Nephritis, Nerve Sheath Neoplasms, Neurilemmoma, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroectodermal Tumors, Primitive, Peripheral, Neuroendocrine Tumors, Neurofibroma, Neurofibromatoses, Neurofibromatosis 1, Neurofibrosarcoma, Neutropenia, Osteosarcoma, Ovarian Diseases, Ovarian Neoplasms, Pancreatic Neoplasms, Pancytopenia, Panuveitis, Parkinson Disease, Pars Planitis, Peripheral Arterial Disease, Peripheral Vascular Diseases, Peritoneal Fibrosis, Peritoneal Neoplasms, Pharyngeal Neoplasms, Pica, Pick Disease of the Brain, Plasmablastic Lymphoma, Plasmacytoma, Pneumonia, Polycystic Kidney Diseases, Polycystic Kidney, Autosomal Dominant, Polyps, Precancerous Conditions, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Preleukemia, Primary Myelofibrosis, Prostatic Neoplasms, Pseudomyxoma Peritonei, Pulmonary Fibrosis, Purpura, Purpura, Thrombocytopenic, Purpura, Thrombocytopenic, Idiopathic, Rage, Rectal Neoplasms, Recurrence, Renal Insufficiency, Renal Insufficiency, Chronic, Retinal Diseases, Retroperitoneal Fibrosis, Retroperitoneal Neoplasms, Rhabdomyosarcoma, Rhabdomyosarcoma, Embryonal, ST Elevation Myocardial Infarction, Sarcoidosis, Sarcoma, Sarcoma, Alveolar Soft Part, Sarcoma, Ewing, Sarcoma, Kaposi, Sarcoma, Synovial, Scleritis, Sclerosis, Severe Acute Respiratory Syndrome, Severe Combined Immunodeficiency, Shy-Drager Syndrome, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Sturge-Weber Syndrome, Syndrome, Telangiectasia, Hereditary Hemorrhagic, Telangiectasis, Thalassemia, Thrombosis, Tongue Neoplasms, Tuberous Sclerosis, Uveitis, Uveitis, Intermediate, Uveitis, Posterior, Vascular Diseases, Vascular Malformations, Vitiligo, Waldenstrom Macroglobulinemia, Wet Macular Degeneration, alpha-Thalassemia, beta-Thalassemia
Erlotinib	BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, CAMK1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BIRC5, BMX, ERBB3, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K1, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, ILK, EGFR, PLK1, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, ERBB4, PAK3, BRAF, FER, CAMKK1, EPHB1, TGFBR2, FYN, PRKD2, NR1I2, RPS6KA4	96	2	Phase 2: Colorectal Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Adenocarcinoma, Bronchiolo-Alveolar, Adenocarcinoma, Mucinous, Adenoma, Adenomatous Polyposis Coli, Adenomatous Polyps, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Brenner Tumor, Carcinoid Tumor, Carcinoma, Carcinoma, Endometrioid, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Cholangiocarcinoma, Cystadenocarcinoma, Cystadenocarcinoma, Mucinous, Cystadenocarcinoma, Serous, Cysts, Diffuse Intrinsic Pontine Glioma, Digestive System Diseases, Endocrine Gland Neoplasms, Ependymoma, Esophageal Diseases, Esophageal Neoplasms, Fallopian Tube Neoplasms, Fibrosarcoma, Gallbladder Neoplasms, Glioblastoma, Glioma, Gliosarcoma, Head and Neck Neoplasms, Hyperkeratosis, Epidermolytic, Ichthyosis, Keratoderma, Palmoplantar, Keratosis, Laryngeal Neoplasms, Leukemia, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myelomonocytic, Acute, Lung Neoplasms, Lymphoma, Lymphoma, Non-Hodgkin, Medulloblastoma, Melanoma, Mesothelioma, Mesothelioma, Malignant, Multiple Endocrine Neoplasia, Multiple Myeloma, Myosarcoma, Nails, Malformed, Nasopharyngeal Neoplasms, Neoplasm Metastasis, Neoplasm Recurrence, Local, Neoplasms, Neoplasms, Unknown Primary, Nerve Sheath Neoplasms, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroendocrine Tumors, Neurofibrosarcoma, Osteosarcoma, Ovarian Neoplasms, Pachyonychia Congenita, Pancreatic Neoplasms, Paranasal Sinus Neoplasms, Pharyngeal Neoplasms, Polycythemia, Polycythemia Vera, Polyps, Precancerous Conditions, Psoriasis, Rectal Neoplasms, Recurrence, Rhabdomyosarcoma, Sarcoma, Sarcoma, Ewing, Small Cell Lung Carcinoma, Thymoma, Thymus Neoplasms, Urinary Bladder Neoplasms, Wilms Tumor

The ***Disease trial phase*** column reflects the maximum clinical trials phase in which the drug was studied for the analyzed pathology.

Repurposing drugs

Table 13. Repurposed drugs used in clinical trials for other pathologies (prospective drugs against the identified drug targets on the basis of literature curation in HumanPSD™ database)
See full table →

Name	Target names	Drug score	Maximum trial phase
seliciclib	BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, CDK4, SYK, EPHA1, CAMK1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, DYRK1A, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, CDK1, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, EEF2K, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFBR2, FYN, PRKD2, RPS6KA4	92	Phase 2: Cystic Fibrosis, Cysts, Fibrosis
1-(5-Tert-Butyl-2-P-Tolyl-2h-Pyrazol-3-Yl)-3-[4-(2-Morpholin-4-Yl-Ethoxy)-Naphthalen-1-Yl]-Urea	BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, CAMK1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, DYRK1A, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, EEF2K, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFBR2, FYN, PRKD2, RPS6KA4	92	Phase 2: Arthritis, Arthritis, Rheumatoid, Psoriasis
pi-103	BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, CAMK1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, DYRK1A, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, EEF2K, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFBR2, FYN, PRKD2, RPS6KA4	92	N/A
ruboxistaurin	BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, CAMK1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, DYRK1A, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, EEF2K, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFBR2, FYN, PRKD2, RPS6KA4	92	Phase 3: Diabetes Mellitus, Diabetes Mellitus, Type 1, Diabetes Mellitus, Type 2, Diabetic Neuropathies, Diabetic Retinopathy, Edema, Macular Edema, Nervous System Diseases, Peripheral Nervous System Diseases, Retinal Diseases
Flavopiridol	BMPR1A, IKBKE, ABL1, FGFR2, NEK7, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, CDK4, SYK, EPHA1, CAMK1, NEK6, EIF2AK2, ERBB2, LIMK1, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, TGFBR1, SRC, CAMKK2, PRKD3, PIP4K2B, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, PIK3CB, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, CDK6, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, ACVR1, DDR2, CHEK1, PTK6, BMX, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, XIAP, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, IRAK3, MAP3K10, SLK, ACVRL1, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, CAMK2B, RPS6KA5, CSK, MAPKAPK5, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, TNIK, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, RPS6KA3, FGFR4, ACVR1B, CAMK2G, MET, PRKCQ, EPHA4, CDK1, LATS1, MAP2K4, PRKAA1, RPS6KA1, FLT4, BMPR2, EGFR, PLK1, PRKCH, ACVR2A, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, LATS2, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, CAMKK1, EPHB1, TGFBR2, FYN, PRKD2, RPS6KA4	92	Phase 2: Embolism, Head and Neck Neoplasms, Lymphoma, Lymphoma, B-Cell, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Neoplasms, Sarcoma, Thromboembolism

The ***Maximum trial phase*** column reflects the maximum clinical trials phase in which the drug was studied for any pathology.

Table 14. Prospective drugs, predicted by PASS software to be active against the identified drug targets with predicted activity against the studied disease(s) (drug candidates predicted with the cheminformatics tool PASS)

See full table →

Name	Target names	Drug score	Target activity score
LE-SN38	HIF1A, TOP2A, CASP3, NFKB1, TOP1, TOP2B	93	3.32
Camptothecin	HIF1A, TOP2A, CASP3, NFKB1, TOP1, TOP2B	93	3.28
Topotecan	HIF1A, TOP2A, CASP3, NFKB1, TOP1, TOP2B	92	3.08
BNP 1350	TOP2A, NFKB1, TOP1, TOP2B	89	2.16
Irinotecan	HIF1A, TOP2A, TOP1, TOP2B	87	1.93

Table 15. Prospective drugs, predicted by PASS software to be active against the identified drug targets, though without cheminformatically predicted activity against the studied disease(s) (drug candidates predicted with the cheminformatics tool PASS)

See full table →

Name	Target names	Drug score	Target activity score
2,6-Dihydroanthra/1,9-Cd/Pyrazol-6-One	IRAK3, PAK2, SENP8, CDK4, SGK1, EPHA1, MAP2K3, CAMK1, CAMK2B, LIMK1, PKN1, MAP2K6, MAPK8, PRKD3, CSNK1G2, DYRK1A, HSP90AB1, CLK4, CSNK1G1, CAMK2A, IRAK1, CHEK2, FES, AKT2, DAPK3, MAPK10, RPS6KA3, IRAK4, CDK6, CAMK2G, CSNK1A1, STAT1, EPHA4, CSNK1E, CDK1, MAP2K4, AURKB, CDK7, PRKAA1, HSP90AA1, CSNK1D, EEF2K, PTK2B, AKT1, AURKA, CHEK1, MAPK9, EPHB2, DYRK1B, GSK3A, PAK4, EPHA3, PAK3, CAMK2D, EPHB1, SGK2, PAK1, CLK1, CDK5, RPS6KA4	96	20.08
Iodophenyl	EIF2AK3, NEK7, PAK2, GSK3B, VRK1, NEK3, NEK6, EIF2AK2, LIMK1, HUNK, MELK, UHMK1, RPS6KB2, CSNK1G2, MAP4K1, VRK2, TRIO, STK11, OBSCN, CSNK1G1, NEK10, KALRN, IRAK1, CSNK2A1, CHEK2, AKT2, PDPK1, STK3, IRAK4, PINK1, CSNK1A1, CSNK1E, RAF1, AURKB, CSNK1D, CHEK1, TAF1, TAOK1, ATM, RIPK2, PIM2, HIPK2, RPS6KA2, PAK4, PIM3, PRKDC, NUAK1, PASK, SGK2, PAK1, CDK5, STK10, ROCK2, BCR, MAK, MAP4K4, CIITA, MARK3, IRAK3, SLK, NEK2, SGK1, TAOK2, RPS6KA5, MAPKAPK5, TNIK, BUB1B, CSNK2A2, TNK2, MAP4K3, RIPK1, STK4, MAP4K2, MAPKAPK2, TAOK3, DAPK3, RPS6KA3, RIPK3, PIK3CG, LATS1, PRKAA1, RPS6KA1, ILK, MASTL, HIPK1, AKT1, AURKA, LMTK2, PKMYT1, RPS6KB1, TBK1, ATR, MTOR, GSK3A, LATS2, PAK3, BRAF, MINK1, RPS6KA4	96	37.44
Rbt205 Inhibitor	RPS6KA3, CDK6, CAMK2G, GRK2, MAP3K10, PRKCQ, PRKACA, GSK3B, PRKCA, CDK1, MAP2K4, CDK4, CDK7, RPS6KA1, PRKAA1, SGK1, PRKCH, EEF2K, CAMK1, CAMK2B, MAPKAPK5, PDP1, PRKD1, PKN1, MAP2K6, RPS6KA2, GSK3A, GRK5, PRKD3, PDP2, PRKCE, PRKCZ, CAMK2D, PTK2, CAMK2A, SIRT1, SGK2, PRKCD, PRKCI, CDK5, PRKACB, DAPK3	95	27.74
Uracil mustard	ABL1, FGFR2, JAK3, INSR, SYK, EPHA1, EIF2AK2, EPHA2, ERBB2, TEK, CSK, AXL, TYK2, MELK, JAK1, IGF1R, SRC, PDGFRB, TNK2, WEE1, PTK2, FLT1, PRKCD, LYN, FES, FGFR4, MET, KDR, EPHA4, PDGFRA, FLT4, MST1R, EGFR, EPHB3, PTK2B, DDR2, PTK6, JAK2, KIT, BMX, RIPK2, ERBB3, EPHB2, FGFR3, MTOR, NTRK2, TYRO3, MERTK, EPHB4, EPHA3, YES1, FGFR1, ERBB4, FER, ITK, EPHB1, FYN, RET, CSF1R, ABL2	94	10.84
7-[4-(Dimethylamino)Phenyl]-N-Hydroxy-4,6-Dimethyl-7-Oxo-2,4-Heptadienamide	HDAC4, HDAC2, HDAC6, HDAC7, HDAC3, HDAC5, HDAC1	94	7.96

As the result of drug search we propose the following drugs as most promising candidates for treating the pathology under study: Sunitinib, seliciclib, LE-SN38 and 2,6-Dihydroanthra/1,9-Cd/Pyrazol-6-One. These drugs were selected for acting on the following targets: INSR, HIF1A and AKT2, which were predicted to be active in the molecular mechanism of the studied pathology.

The selected drugs are top ranked drug candidates from each of the four categories of drugs: (1) FDA approved drugs or used in clinical trials drugs for the studied pathology; (2) repurposing drugs used in clinical trials for other pathologies; (3) drugs, predicted by PASS software to be active against the studied pathology; (4) drugs, predicted by PASS software to be repurposed from other pathologies.

Supplementary drug info

In addition to the approved and repurposed drugs proposed by Genome Enhancer, below the ***Supplementary drug info*** table is given, which contains an extended list of drugs used for treatment of neoplasms. Those drugs which were predicted by Genome Enhancer as prospective treatment candidates for the studied case (both approved and repurposed) have a respective ***Predicted Drug Score*** assigned to them. This value on a scale from 1 to 100 reflects the potential activity of the respective drug on the overall molecular mechanism of the studied pathology. The ***Predicted Drug Score*** column contains the "-" (Not Identified) value in case the drug targets of the respective treatment were not found in the molecular mechanism of the studied pathology.

Table 16. Supplementary drug info: extended list of drugs used for treatment of neoplasms with respective drug scores predicted for the studied pathology.

Drug	Disease	Predicted Drug Score	Somatic variants
Abarelix	Prostatic Neoplasms	8	
abemaciclib	Breast Neoplasms	67	
Abiraterone	Prostatic Neoplasms, Castration-Resistant	-	
abiraterone acetate	Prostatic Neoplasms|Prostatic Neoplasms, Castration-Resistant	-	
acalabrutinib	Lymphoma, Mantle-Cell	37	
Acetaminophen	Acute Pain|Arthritis|Back Pain|Brain Injuries|Common Cold|Dysmenorrhea|Fever|Headache|Hernia, Abdominal|Hypertension|Infections|Influenza, Human|Meningitis, Bacterial|Migraine Disorders|Muscle Cramp|Nausea|Neoplasms|Obesity|Obesity, Morbid|Osteoarthritis|Osteoarthritis, Knee|Pain|Pharyngitis|Postoperative Nausea and Vomiting|Streptococcal Infections|Thrombotic Stroke|Tonsillitis|Toothache|Vomiting|Wounds and Injuries	55	
Acetylsalicylic acid	Acute Coronary Syndrome|Arthritis|Asthma|Atherosclerosis|Atrial Fibrillation|Back Pain|Cardiovascular Diseases|Cerebral Infarction|Common Cold|Coronary Artery Disease|Coronary Disease|Diabetes Mellitus|Diabetes Mellitus, Type 2|Dysmenorrhea|Fever|Headache|Heart Diseases|Heart Failure|Hypertension|Internal Hernia|Ischemia|Migraine Disorders|Muscle Cramp|Myalgia|Myocardial Infarction|Myocardial Ischemia|Neoplasms|Pain|Peptic Ulcer|Periodontitis|Placental Insufficiency|Pre-Eclampsia|Scleroderma, Diffuse|Scleroderma, Systemic|Sclerosis|Spasm|ST Elevation Myocardial Infarction|Stroke|Thrombosis|Toothache|Ulcer|Vascular Diseases	84	

ado-trastuzumab emtansine	Breast Neoplasms	83
Afatinib	Carcinoma, Non-Small-Cell Lung	80
afatinib dimaleate	Carcinoma, Non-Small-Cell Lung	-
Aflibercept	Colorectal Neoplasms|Macular Degeneration|Macular Edema|Retinal Detachment|Retinal Diseases|Retinal Vein Occlusion|Wet Macular Degeneration	61
Aldesleukin	Carcinoma|Carcinoma, Renal Cell|Melanoma	40
Alectinib	Carcinoma, Non-Small-Cell Lung	76
Alemtuzumab	Leukemia, Lymphocytic, Chronic, B-Cell|Nerve Degeneration	-
Alfuzosin	Prostatic Hyperplasia	-
Alitretinoin	Sarcoma, Kaposi	57
Allopurinol	Bipolar Disorder|Colitis-Associated Neoplasms|Diabetes Mellitus|Gout|Heart Failure|Hypertension|Hyperuricemia|Internal Hernia|Ischemia|Leukemia|Lymphoma|Neoplasms|Response Evaluation Criteria in Solid Tumors|Stroke	-
alpelisib	Breast Neoplasms	-
Altretamine	Ovarian Neoplasms	-
Amifostine	Head and Neck Neoplasms|Neoplasms|Ovarian Neoplasms|Xerostomia	56
Aminoglutethimide	Neoplasms	-
amivantamab	Carcinoma, Non-Small-Cell Lung	60
Amphotericin B	Aspergillosis|Candidiasis|Candidiasis, Invasive|Cryptococcosis|Histoplasmosis|Infections|Leishmaniasis|Leishmaniasis, Visceral|Leukemia|Meningitis, Cryptococcal|Mucormycosis|Mycoses|Sporotrichosis|Zygomycosis	-
Amsacrine	Neoplasms	49
Anastrozole	Breast Neoplasms|Endometriosis|Hypogonadism|Neoplasms	51
apalutamide	Prostatic Neoplasms, Castration-Resistant	14
Aprepitant	Breast Neoplasms|Nausea|Neoplasms|Postoperative Nausea and Vomiting|Vomiting	-
Aripiprazole	Alcoholism|Alzheimer Disease|Anxiety|Attention Deficit Disorder with Hyperactivity|Autistic Disorder|Bipolar Disorder|Child Development Disorders, Pervasive|Colitis-Associated Neoplasms|Depressive Disorder|Depressive Disorder, Major|Psychotic Disorders|Schizophrenia|Tourette Syndrome|Weight Loss	-
Arsenic trioxide	Leukemia, Promyelocytic, Acute	82
arzoxifene	Endometrial Neoplasms	28
asciminib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	44
Asparaginase Erwinia chrysanthemi	Precursor Cell Lymphoblastic Leukemia-Lymphoma	-
atezolizumab	Carcinoma, Non-Small-Cell Lung|Carcinoma, Transitional Cell|Triple Negative Breast Neoplasms	-
avapritinib	Gastrointestinal Stromal Tumors|Neoplasms	75
avelumab	Carcinoma, Merkel Cell|Carcinoma, Renal Cell|Carcinoma, Transitional Cell	-
Avobenzone	Melanosis|Skin Neoplasms|Sunburn	-
Axitinib	Carcinoma, Renal Cell	93
Azacitidine	Anemia, Refractory|Anemia, Refractory, with Excess of Blasts|Leukemia|Leukemia, Myelomonocytic, Chronic|Myelodysplastic Syndromes	67
Azithromycin	Asthma|Blepharitis|Bronchiectasis|Bronchiolitis|Bronchiolitis Obliterans|Bronchopulmonary Dysplasia|Chlamydia Infections|COVID-19|Cystic Fibrosis|Diarrhea|Endometritis|Eye Diseases|Fever|Gonorrhea|Infections|Lung Diseases|Malnutrition|Mycobacterium avium-intracellulare Infection|Otitis Media|Pharyngitis|Pneumonia|Premature Birth|Pulmonary Disease, Chronic Obstructive|Sepsis|Sinusitis|Skin Diseases, Infectious|Tonsillitis|Urethritis|Uterine Cervicitis|Yaws	-
belantamab mafodotin	Multiple Myeloma|Neoplasms	-
Belinostat	Lymphoma, T-Cell, Peripheral	84
belzutifan	Carcinoma, Renal Cell|Hemangioblastoma|Neuroendocrine Tumors|von Hippel-Lindau Disease	48
Bendamustine	Leukemia|Leukemia, Lymphocytic, Chronic, B-Cell	-
Bevacizumab	Colorectal Neoplasms	65
Bexarotene	Lymphoma|Lymphoma, T-Cell, Cutaneous	64
Bicalutamide	Neoplasms|Prostatic Neoplasms	68
binimetinib	Melanoma	66
Blinatumomab	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	-
Bortezomib	Multiple Myeloma|Neoplasms|Renal Insufficiency, Chronic	73
Bosutinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	83
Brentuximab vedotin	Hodgkin Disease|Lymphoma, Large-Cell, Anaplastic|Lymphoma, T-Cell, Peripheral	-
brigatinib	Carcinoma, Non-Small-Cell Lung	70
Bupivacaine	Anesthesia|Ankle Fractures|Appendicitis|Brain Neoplasms|Dwarfism|Fractures, Bone|Hallux Valgus|Headache|Hemorrhage|Hemorrhoids|Hernia|Hernia, Inguinal|Hypotension|Migraine Disorders|Neoplasms|Neuralgia|Obesity|Obesity, Morbid|Opioid-Related Disorders|Osteoarthritis|Osteoarthritis, Hip|Osteoarthritis, Knee|Pain|Rib Fractures|Rotator Cuff Injuries|Thoracic Injuries|Thrombotic Stroke|Wounds and Injuries	28
Bupropion	Alcoholism|Attention Deficit Disorder with Hyperactivity|Depressive Disorder|Depressive Disorder, Major|Lung Neoplasms|Mood Disorders|Neoplasms|Schizophrenia|Substance-Related Disorders|Tobacco Use Disorder	-
Buserelin	Prostatic Neoplasms	-
Busulfan	Leukemia|Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Neoplasms	-
Cabazitaxel	Neoplasms|Prostatic Neoplasms|Prostatic Neoplasms, Castration-Resistant	77
Cabergoline	Infertility|Infertility, Female|Pituitary Neoplasms	19
Cabozantinib	Thyroid Neoplasms	85
Capecitabine	Adenocarcinoma|Breast Neoplasms|Colonic Neoplasms|Colorectal Neoplasms|Neoplasms|Rectal Neoplasms	21

capivasertib	Breast Neoplasms	90	
capmatinib	Carcinoma, Non-Small-Cell Lung	87	
Carbamazepine	Bipolar Disorder|Cocaine-Related Disorders|Colitis-Associated Neoplasms|Depressive Disorder|Epilepsies, Partial|Epilepsy|Glossopharyngeal Nerve Diseases|Seizures|Trigeminal Neuralgia	6	
Carboplatin	Breast Neoplasms|Ovarian Neoplasms	-	XRCC1:Q399R:sensitivity/response:B2
Carfilzomib	Brain Abscess|Multiple Myeloma|Neoplasms|Neoplasms, Plasma Cell	78	
Carmustine	Astrocytoma|Ependymoma|Glioblastoma|Glioma|Hodgkin Disease|Medulloblastoma|Multiple Myeloma|Neoplasms	35	
Celecoxib	Arthritis, Rheumatoid|Hypertension|Inflammation|Low Back Pain|Neoplasms|Osteoarthritis|Osteoarthritis, Hip|Osteoarthritis, Knee|Rectal Neoplasms|Spondylitis, Ankylosing|Wounds and Injuries	53	
cemiplimab	Carcinoma, Basal Cell|Carcinoma, Squamous Cell|Lung Neoplasms|Neoplasms|Skin Neoplasms	22	
Ceritinib	Carcinoma, Non-Small-Cell Lung	87	
Cetuximab	Colorectal Neoplasms	48	
Chlorambucil	Hodgkin Disease|Neoplasms|Precursor Cell Lymphoblastic Leukemia-Lymphoma	19	
Chlorotrianisene	Carcinoma, Hepatocellular	38	
Choline C 11	Prostatic Neoplasms	-	
Cinacalcet	Hyperparathyroidism, Primary|Hyperparathyroidism, Secondary|Parathyroid Neoplasms|Renal Insufficiency, Chronic	-	
Cladribine	Brain Abscess|Leukemia|Leukemia, Hairy Cell|Multiple Sclerosis|Sclerosis	78	
Clarithromycin	Bacterial Infections|Bronchitis, Chronic|Duodenal Ulcer|Helicobacter Infections|Infections|Mycobacterium avium-intracellulare Infection|Neoplasms|Otitis Media|Periodontitis|Pharyngitis|Pneumonia|Sinusitis|Skin Diseases, Bacterial|Stomach Neoplasms|Tonsillitis|Tuberculosis	10	
Clofarabine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	78	
Clonidine	Attention Deficit Disorder with Hyperactivity|Cardiovascular Diseases|Glaucoma|Hypertension|Migraine Disorders|Neoplasms|Neuralgia	-	
Cobimetinib	Melanoma	82	
copanlisib	Lymphoma, Follicular	87	
Cortisone acetate	Addison Disease|Adrenal Hyperplasia, Congenital|Anemia, Aplastic|Anemia, Hemolytic|Arthritis, Gouty|Arthritis, Juvenile|Arthritis, Psoriatic|Arthritis, Rheumatoid|Asthma|Bursitis|Dermatitis Herpetiformis|Dermatitis, Atopic|Dermatitis, Contact|Dermatitis, Exfoliative|Dermatitis, Seborrheic|Dermatomyositis|Enteritis|Erythema Multiforme|Eye Diseases|Herpes Zoster Ophthalmicus|Hypercalcemia|Hypersensitivity|Iridocyclitis|Iritis|Leukemia|Lupus Erythematosus, Systemic|Lymphoma|Nephrotic Syndrome|Ophthalmia, Sympathetic|Osteoarthritis|Peptic Ulcer|Pneumonia|Polymyositis|Purpura, Thrombocytopenic, Idiopathic|Stevens-Johnson Syndrome|Synovitis|Tennis Elbow|Tenosynovitis|Thrombocytopenia|Thyroiditis, Subacute|Tuberculosis, Meningeal|Tuberculosis, Pulmonary|Uveitis, Posterior	21	
CP-4055	Leukemia, Myeloid, Acute	-	
Crizotinib	Carcinoma, Non-Small-Cell Lung	92	
Cyclophosphamide	Breast Neoplasms|Hodgkin Disease|Lupus Nephritis|Lymphoma|Lymphoma, Non-Hodgkin|Multiple Myeloma|Neoplasms|Nephrotic Syndrome	78	
Cyclosporine	Acute Kidney Injury|Anemia|Anemia, Aplastic|Arthritis, Rheumatoid|Conjunctivitis, Allergic|COVID-19|Dermatitis, Atopic|Diabetes Mellitus|Dry Eye Syndromes|Eczema|Eye Diseases|Graft vs Host Disease|Immune System Diseases|Infections|Inflammation|Keratoconjunctivitis|Keratoconjunctivitis Sicca|Leukemia|Meibomian Gland Dysfunction|Myelodysplastic Syndromes|Neoplasms|Psoriasis|Pterygium|Renal Insufficiency|Renal Insufficiency, Chronic|Stevens-Johnson Syndrome|Uveitis	77	
Cyproterone acetate	Prostatic Neoplasms	12	
Cytarabine	Leukemia|Leukemia, Lymphoid|Leukemia, Myeloid, Acute|Leukemia, Promyelocytic, Acute|Meningeal Carcinomatosis|Neoplasms|Precursor Cell Lymphoblastic Leukemia-Lymphoma	83	
Dabrafenib	Melanoma	55	
Dacarbazine	Hodgkin Disease|Melanoma|Neoplasms	49	
dacomitinib	Carcinoma, Non-Small-Cell Lung	84	
Dactinomycin	Neoplasms|Wilms Tumor	76	
Daratumumab	Multiple Myeloma	-	
darolutamide	Neoplasms|Prostatic Neoplasms|Prostatic Neoplasms, Castration-Resistant	8	
Dasatinib	Leukemia|Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Leukemia, Myeloid|Precursor Cell Lymphoblastic Leukemia-Lymphoma	96	
Daunorubicin	Leukemia|Leukemia, Lymphoid|Leukemia, Myeloid, Acute|Neoplasms	57	
Decitabine	Anemia, Refractory|Anemia, Refractory, with Excess of Blasts|Leukemia, Myelomonocytic, Chronic|Myelodysplastic Syndromes	65	
Degarelix	Neoplasms|Prostatic Neoplasms	71	
Dehydroepiandrosterone	Arthritis, Rheumatoid|Dysmenorrhea|Hypogonadism|Infertility|Klinefelter Syndrome|Neoplasms|Orchitis|Osteoarthritis|Pain	76	
Denileukin diftitox	Lymphoma, T-Cell, Cutaneous	39	
Dexamethasone	Acne Vulgaris|Addison Disease|Adrenal Hyperplasia, Congenital|Adrenal Insufficiency|Adrenocortical Hyperfunction|Anemia, Aplastic|Anemia, Hemolytic|Arthritis, Gouty|Arthritis, Juvenile|Arthritis, Psoriatic|Arthritis, Rheumatoid|Asthma|Brain Edema|Bursitis|Cataract|Chorioretinitis|Choroiditis|Colitis, Ulcerative|Conjunctivitis, Allergic|Corneal Injuries|COVID-19|Crohn Disease|Dermatitis|Dermatitis Herpetiformis|Dermatitis, Atopic|Dermatitis, Contact|Dermatitis, Exfoliative|Dermatitis, Seborrheic|Diabetic Retinopathy|Erythema Multiforme|Eye Diseases|Hemorrhoids|Herpes Simplex|Herpes Zoster Ophthalmicus|Hypercalcemia|Infections|Inflammation|Iridocyclitis|Iritis|Keratitis|Laryngeal Edema|Leukemia|Lupus Erythematosus, Systemic|Lymphoma|Macular Edema|Multiple Myeloma|Multiple Sclerosis|Mycosis Fungoides|Myocarditis|Nasal Obstruction|Nausea|Neoplasms|Nephrotic Syndrome|Ophthalmia, Sympathetic|Optic	84	

	Neuritis|Osteoarthritis|Pemphigus|Peptic Ulcer|Pneumonia|Postoperative Nausea and Vomiting|Psoriasis|Pulmonary Eosinophilia|Purpura, Thrombocytopenic, Idiopathic|Respiratory Insufficiency|Retinal Vein Occlusion|Rhinitis, Allergic|Rhinitis, Allergic, Seasonal|Sarcoidosis|Serum Sickness|Spondylitis, Ankylosing|Stevens-Johnson Syndrome|Synovitis|Tennis Elbow|Tenosynovitis|Thrombocytopenia|Thyroiditis, Subacute|Transfusion Reaction|Trichinellosis|Tuberculosis, Meningeal|Tuberculosis, Pulmonary|Uveitis, Intermediate|Uveitis, Posterior|Vomiting	
dexamethasone sodium phosphate	Acne Vulgaris|Addison Disease|Adrenal Hyperplasia, Congenital|Adrenal Insufficiency|Anemia, Aplastic|Anemia, Hemolytic|Arthritis, Gouty|Arthritis, Juvenile|Arthritis, Psoriatic|Arthritis, Rheumatoid|Asthma|Brain Edema|Bursitis|Chorioretinitis|Choroiditis|Colitis, Ulcerative|Conjunctivitis, Allergic|Corneal Injuries|Crohn Disease|Dermatitis|Dermatitis Herpetiformis|Dermatitis, Atopic|Dermatitis, Contact|Dermatitis, Exfoliative|Dermatitis, Seborrheic|Erythema Multiforme|Eye Diseases|Hemorrhoids|Herpes Simplex|Herpes Zoster Ophthalmicus|Hypercalcemia|Inflammation|Iridocyclitis|Iritis|Keratitis|Laryngeal Edema|Leukemia|Lupus Erythematosus, Systemic|Lymphoma|Macular Edema|Multiple Myeloma|Mycosis Fungoides|Myocarditis|Nasal Obstruction|Neoplasms|Nephrotic Syndrome|Ophthalmia, Sympathetic|Optic Neuritis|Osteoarthritis|Pemphigus|Peptic Ulcer|Pneumonia|Psoriasis|Pulmonary Eosinophilia|Purpura, Thrombocytopenic, Idiopathic|Rhinitis, Allergic|Rhinitis, Allergic, Seasonal|Sarcoidosis|Serum Sickness|Spondylitis, Ankylosing|Stevens-Johnson Syndrome|Synovitis|Tennis Elbow|Tenosynovitis|Thrombocytopenia|Thyroiditis, Subacute|Transfusion Reaction|Trichinellosis|Tuberculosis, Meningeal|Tuberculosis, Pulmonary|Uveitis, Posterior	-
Dexmedetomidine	Acute Kidney Injury|Brain Neoplasms|Cognitive Dysfunction|Cough|Delirium|Heart Diseases|Heart Septal Defects, Atrial|Hypertension|Inflammation|Neoplasms|Pain|Postoperative Cognitive Complications|Psychomotor Agitation|Psychotic Disorders|Respiratory Insufficiency|Shock, Septic|Stomach Neoplasms|Wounds and Injuries	-
Dexrazoxane	Breast Neoplasms|Cardiomyopathies	60
Docetaxel	Breast Neoplasms|Carcinoma|Carcinoma, Non-Small-Cell Lung|Carcinoma, Squamous Cell|Head and Neck Neoplasms|Lung Neoplasms|Neoplasms|Prostatic Neoplasms|Squamous Cell Carcinoma of Head and Neck|Stomach Neoplasms	80
Dolasetron	Nausea|Neoplasms|Postoperative Nausea and Vomiting	-
Donepezil	Alzheimer Disease|Amblyopia|Aphasia|Cognitive Dysfunction|Colitis-Associated Neoplasms|Delirium|Dementia|Dementia, Vascular|Multiple Sclerosis|Parkinson Disease|Stroke	12
dostarlimab	Endometrial Neoplasms|Neoplasms	22
Doxazosin	Hypertension|Prostatic Hyperplasia|Stress Disorders, Post-Traumatic	-
Doxercalciferol	Hyperparathyroidism, Secondary|Kidney Diseases|Neoplasms|Renal Insufficiency, Chronic	72
doxifluridine	Breast Neoplasms|Colonic Neoplasms|Neoplasms|Stomach Neoplasms	19
Doxorubicin	Breast Neoplasms|Carcinoma|Carcinoma, Hepatocellular|Carcinoma, Ovarian Epithelial|Heart Failure|Hodgkin Disease|Leukemia, Myelomonocytic, Acute|Lymphoma|Lymphoma, Non-Hodgkin|Multiple Myeloma|Neoplasms|Osteosarcoma|Ovarian Neoplasms|Sarcoma|Sarcoma, Kaposi|Urinary Bladder Neoplasms	92
durvalumab	Carcinoma, Non-Small-Cell Lung|Carcinoma, Transitional Cell	-
Dutasteride	Hypogonadism|Prostatic Hyperplasia|Prostatic Neoplasms	-
duvelisib	Leukemia, Lymphocytic, Chronic, B-Cell|Lymphoma, Follicular	75
elacestrant	Breast Neoplasms	38
Elotuzumab	Multiple Myeloma	73
elranatamab	Multiple Myeloma	-
enasidenib	Leukemia, Myeloid, Acute	-
encorafenib	Colorectal Neoplasms|Melanoma	86
enfortumab vedotin	Carcinoma, Transitional Cell|Neoplasms	-
entrectinib	Carcinoma, Non-Small-Cell Lung	60
Enzalutamide	Neoplasms|Prostatic Neoplasms|Prostatic Neoplasms, Castration-Resistant	15
epcoritamab	Lymphoma, Large B-Cell, Diffuse	-
Epirubicin	Breast Neoplasms	75
erdafitinib	Urinary Bladder Neoplasms	91
Ergocalciferol	Bone Diseases, Metabolic|Crohn Disease|Cysts|Diabetes Mellitus, Type 2|Fractures, Bone|Heart Failure|Hip Fractures|Hypoparathyroidism|Hypophosphatemia, Familial|Insulin Resistance|Muscular Diseases|Neoplasms|Osteoporosis|Polycystic Ovary Syndrome|Renal Insufficiency, Chronic|Rickets, Hypophosphatemic|Syndrome|Vitamin D Deficiency	44
Eribulin	Breast Neoplasms|Neurotoxicity Syndromes	-
Erlotinib	Carcinoma, Non-Small-Cell Lung|Neoplasms	96
Esomeprazole	Arthritis, Rheumatoid|Croup|Digestive System Diseases|Duodenal Ulcer|Dyspepsia|Esophagitis|Esophagitis, Peptic|Gastritis|Gastroesophageal Reflux|Gastrointestinal Diseases|Helicobacter Infections|Hemorrhage|Intestinal Diseases|Neoplasms|Osteoarthritis|Peptic Ulcer|Spondylitis, Ankylosing|Stomach Ulcer|Ulcer|Zollinger-Ellison Syndrome	-
Estradiol	Atrophic Vaginitis|Atrophy|Breast Neoplasms|Dyspareunia|Hypogonadism|Menopause|Osteoporosis|Osteoporosis, Postmenopausal|Primary Ovarian Insufficiency	69
Estramustine	Prostatic Neoplasms	63
estramustine phosphate	Carcinoma|Neoplasms	-
Ethinyl Estradiol	Acne Vulgaris|Neoplasms	60
Etoposide	Carcinoma, Small Cell|Lung Neoplasms|Neoplasms|Small Cell Lung Carcinoma	82
Everolimus	Angiomyolipoma|Astrocytoma|Breast Neoplasms|Carcinoma|Carcinoma, Renal Cell|Kidney Diseases|Neoplasms|Neuroendocrine Tumors|Polycystic Kidney Diseases|Polycystic Kidney, Autosomal Dominant|Renal Insufficiency|Renal Insufficiency, Chronic|Tuberous Sclerosis	86
Exemestane	Breast Neoplasms|Neoplasms	-

Fentanyl	Acute Pain|Chronic Pain|Hemorrhage|Hyperalgesia|Low Back Pain|Migraine Disorders|Neoplasms|Neuralgia|Pain|Respiratory Insufficiency	-
Finasteride	Prostatic Hyperplasia|Prostatic Neoplasms	46
Flavopiridol	Leukemia, Lymphocytic, Chronic, B-Cell	92
Floxuridine	Neoplasms	78
Fludarabine	Leukemia, Lymphocytic, Chronic, B-Cell	82
fluoroestradiol f-18	Breast Neoplasms	-
Fluorouracil	Adenocarcinoma|Carcinoma|Carcinoma, Basal Cell|Carcinoma, Squamous Cell|Colonic Neoplasms|Colorectal Neoplasms|Esophageal Neoplasms|Glaucoma|Keratosis|Keratosis, Actinic|Neoplasms|Rectal Neoplasms	82
Fluoxymesterone	Breast Neoplasms|Hypogonadism|Puberty, Delayed	42
Flutamide	Prostatic Neoplasms	72
Formestane	Neoplasms	-
Fosaprepitant	Neoplasms|Postoperative Nausea and Vomiting	-
fruquintinib	Colorectal Neoplasms	80
Fulvestrant	Breast Neoplasms|Neoplasms	69
futibatinib	Cholangiocarcinoma	83
Gefitinib	Carcinoma, Non-Small-Cell Lung|Lung Neoplasms|Neoplasms	91
Gemcitabine	Breast Neoplasms|Carcinoma, Non-Small-Cell Lung|Neoplasms|Ovarian Neoplasms|Pancreatic Neoplasms	82
Gemtuzumab ozogamicin	Leukemia, Myeloid, Acute	25
gilteritinib	Leukemia, Myeloid, Acute	78
glasdegib	Leukemia, Myeloid, Acute	16
glofitamab	Lymphoma, Large B-Cell, Diffuse	43
Goserelin	Breast Neoplasms|Endometriosis|Infertility|Leiomyoma|Neoplasms|Prostatic Neoplasms	-
Guanidine	Carcinoma, Small Cell|Lambert-Eaton Myasthenic Syndrome|Muscle Weakness	16
Hexaminolevulinate	Carcinoma	-
histrelin	Neoplasms	-
Homoharringtonine	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	84
Hydrocortisone	Adrenal Hyperplasia, Congenital|Arthritis, Juvenile|Arthritis, Psoriatic|Arthritis, Rheumatoid|Asthma|Bursitis|Colitis, Ulcerative|Conjunctivitis, Allergic|Crohn Disease|Dermatitis|Dermatitis, Atopic|Dermatitis, Seborrheic|Eczema|Endocrine System Diseases|Exanthema|Eye Diseases|Hemorrhoids|Herpes Labialis|Inflammation|Intertrigo|Leukemia|Lymphoma|Nasal Obstruction|Neoplasms|Osteoarthritis|Otitis Externa|Pneumonia|Pruritus|Psoriasis|Serum Sickness|Shock, Septic|Skin Diseases|Spondylitis|Tenosynovitis|Wounds and Injuries	80
Hydromorphone	Acute Pain|Low Back Pain|Neoplasms|Pain|Substance-Related Disorders	-
hydroxyflutamide	Carcinoma|Neoplasms|Prostatic Neoplasms	-
Hydroxyurea	Anemia, Sickle Cell|Carcinoma, Squamous Cell|Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Melanoma|Neoplasms	66
Ibandronate	Bone Diseases|Bone Diseases, Metabolic|Bone Neoplasms|Neoplasm Metastasis|Osteoporosis|Osteoporosis, Postmenopausal	6
Ibritumomab	Lymphoma, B-Cell|Lymphoma, Follicular	25
Ibrutinib	Graft vs Host Disease|Leukemia, Lymphocytic, Chronic, B-Cell|Lymphoma, B-Cell, Marginal Zone|Lymphoma, Mantle-Cell|Waldenstrom Macroglobulinemia	87
icotinib	Carcinoma, Non-Small-Cell Lung|Lung Neoplasms|Neoplasms	32
Idarubicin	Leukemia, Myeloid, Acute	51
Idelalisib	Leukemia, Lymphocytic, Chronic, B-Cell|Lymphoma, Follicular	77
Ifosfamide	Neoplasms|Testicular Neoplasms	55
Imatinib	Gastrointestinal Stromal Tumors|Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Neoplasms	91
imatinib mesylate	Breast Neoplasms|Gastrointestinal Stromal Tumors|Leukemia|Leukemia, Myelogenous, Chronic, BCR-ABL Positive	-
Imiquimod	Carcinoma, Basal Cell|Cheilitis|Condylomata Acuminata|Keratosis, Actinic|Lentigo	47
infigratinib	Cholangiocarcinoma	75
inositol	Colitis-Associated Neoplasms	70
inotuzumab ozogamicin	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	-
Interferon Alfa-2a, Recombinant	Leukemia, Hairy Cell	63
Interferon Alfa-2b, Recombinant	Leukemia, Hairy Cell	63
Iopamidol	Glioma|Pituitary Neoplasms	-
ipilimumab	Carcinoma, Renal Cell|Melanoma	41
Irinotecan	Colorectal Neoplasms	75
isatuximab	Multiple Myeloma|Neoplasms	14
Isopropyl Alcohol	Acromegaly|Anemia|Arthritis, Psoriatic|Arthritis, Rheumatoid|Burns|Colitis, Ulcerative|Constipation|Eczema|Infections|Multiple Sclerosis|Prostatic Neoplasms|Psoriasis|Spondylitis, Ankylosing	-
ivosidenib	Leukemia, Myeloid, Acute	-
Ixabepilone	Breast Neoplasms	-
Ixazomib	Multiple Myeloma	-
Ketamine	Delirium|Depression, Postpartum|Depressive Disorder|Depressive Disorder, Major|Fractures, Bone|Hemorrhage|Lung Neoplasms|Neoplasms|Opioid-Related Disorders|Pain|Postoperative Complications|Suicidal Ideation	-
Lamotrigine	Bipolar Disorder|Cocaine-Related Disorders|Colitis-Associated Neoplasms|Depressive Disorder|Epilepsies, Partial|Epilepsy|Epilepsy, Tonic-Clonic|Mental Disorders|Mood Disorders|Seizures	-
Lanreotide	Acromegaly|Neoplasms	-
Lapatinib	Breast Neoplasms	92
larotrectinib	Neoplasm Metastasis	54
LE-SN38	Adenocarcinoma|Carcinoma|Neoplasms	38

Lenalidomide	Multiple Myeloma|Myelodysplastic Syndromes|Neoplasms	63
Lenvatinib	Carcinoma, Hepatocellular|Carcinoma, Renal Cell|Thyroid Neoplasms	94
Letrozole	Anovulation|Breast Neoplasms|Cardiac Complexes, Premature|Infertility|Leiomyoma|Neoplasms|Polycystic Ovary Syndrome|Pregnancy, Ectopic	25
Leuprolide	Endometriosis|Infertility|Neoplasms|Prostatic Neoplasms|Puberty, Precocious	-
Levamisole	Colonic Neoplasms|Helminthiasis	-
Levetiracetam	Alcoholism|Bipolar Disorder|Brain Neoplasms|Colitis-Associated Neoplasms|Epilepsies, Partial|Epilepsy|Parkinson Disease|Polyneuropathies|Seizures	-
Levobupivacaine	Muscle Weakness|Neoplasms|Paresis	-
levoleucovorin	Anemia|Colorectal Neoplasms|Osteosarcoma	-
Levonorgestrel	Endometrial Hyperplasia|Endometriosis|Hemorrhage|Menorrhagia	43
Levothyroxine	Congenital Hypothyroidism|Hypothyroidism|Thyroid Neoplasms	39
Lidocaine	Anesthesia|Arrhythmias, Cardiac|Arthritis|Back Pain|Burns|Bursitis|Hemorrhoids|Inflammation|Insect Bites and Stings|Muscle Cramp|Myalgia|Neuralgia|Neuralgia, Postherpetic|Osteoarthritis|Pain|Premature Ejaculation|Prostatic Neoplasms|Pruritus|Rectal Diseases|Sprains and Strains|Sunburn|Tendinopathy|Urethritis	9
lidocaine patch	Breast Neoplasms|Lung Diseases|Pneumonia	-
Liothyronine	Depressive Disorder|Hypothyroidism|Myxedema|Thyroid Neoplasms	53
lipegfilgrastim	Neoplasms	-
Lomustine	Brain Neoplasms|Hodgkin Disease	-
loncastuximab tesirine	Lymphoma, B-Cell|Lymphoma, Large B-Cell, Diffuse	-
lorlatinib	Carcinoma, Non-Small-Cell Lung	76
lurbinectedin	Neoplasms|Small Cell Lung Carcinoma	-
margetuximab	Breast Neoplasms	38
Mechlorethamine	Lymphoma, T-Cell, Cutaneous|Neoplasms	-
Medroxyprogesterone Acetate	Carcinoma, Renal Cell|Endometriosis|Hemorrhage|Hyperplasia|Infertility|Neoplasms|Uterine Hemorrhage	71
Megestrol acetate	Acquired Immunodeficiency Syndrome|Anorexia|Breast Neoplasms|Cachexia	58
Melphalan	Carcinoma|Multiple Myeloma|Neoplasms	63
melphalan flufenamide	Multiple Myeloma	79
Mercaptopurine	Leukemia|Leukemia, Lymphoid|Lymphoma|Neoplasms|Precursor Cell Lymphoblastic Leukemia-Lymphoma	-
Mesna	Neoplasms|Thrombocytopenia	-
Methadone	Acute Pain|Heroin Dependence|HIV Infections|Neonatal Abstinence Syndrome|Neoplasms|Neuralgia|Opioid-Related Disorders|Pain|Scoliosis|Substance-Related Disorders	-
Methotrexate	Adenoma|Arthritis|Arthritis, Juvenile|Arthritis, Psoriatic|Arthritis, Rheumatoid|Breast Neoplasms|Choriocarcinoma|Communicable Diseases|Crohn Disease|Gout|Immune System Diseases|Lung Neoplasms|Lymphoma|Lymphoma, Non-Hodgkin|Meningeal Carcinomatosis|Multiple Sclerosis|Mycosis Fungoides|Neoplasms|Osteoarthritis|Precursor Cell Lymphoblastic Leukemia-Lymphoma|Pregnancy, Ectopic|Psoriasis|Uveitis	69
Methoxsalen	Lymphoma|Lymphoma, T-Cell|Mycosis Fungoides|Psoriasis	6
Methyl aminolevulinate	Glioma|Keratosis, Actinic|Neoplasms	-
Methylphenidate	Alcoholism|Alzheimer Disease|Attention Deficit Disorder with Hyperactivity|Bipolar Disorder|Brain Injuries|Brain Neoplasms|Cocaine-Related Disorders|Dementia|Depressive Disorder|Narcolepsy|Neoplasms|Parkinson Disease|Substance-Related Disorders	-
Methylprednisolone	Acne Vulgaris|Anemia|Arthritis, Juvenile|Arthritis, Psoriatic|Arthritis, Rheumatoid|Asthma|Bursitis|Colitis, Ulcerative|Crohn Disease|Dermatitis|Dermatitis, Atopic|Endocrine System Diseases|Fasciitis, Plantar|Inflammation|Leukemia|Lymphoma|Multiple Sclerosis|Multiple Sclerosis, Relapsing-Remitting|Osteoarthritis|Pneumonia|Purpura, Thrombocytopenic, Idiopathic|Serum Sickness|Tenosynovitis|Uveitis, Posterior	64
Methyltestosterone	Breast Neoplasms|Hypogonadism|Puberty, Delayed	-
Metoclopramide	Anorexia|Digestive System Diseases|Gastroparesis|Heartburn|Nausea|Neoplasms|Postoperative Nausea and Vomiting|Renal Insufficiency|Vomiting	-
midostaurin	Leukemia, Mast-Cell|Leukemia, Myeloid, Acute|Mastocytosis, Systemic	92
mirvetuximab soravtansine	Ovarian Neoplasms	-
Mitomycin	Adenocarcinoma|Glaucoma|Glaucoma, Neovascular|Glaucoma, Open-Angle|Myopia|Neoplasms	75
Mitotane	Adrenocortical Carcinoma	47
Mitoxantrone	Leukemia, Myeloid, Acute|Multiple Sclerosis|Prostatic Neoplasms, Castration-Resistant	77
mobocertinib	Carcinoma, Non-Small-Cell Lung	59
mogamulizumab	Mycosis Fungoides|Neoplasms|Sezary Syndrome	-
Morphine	Abdominal Neoplasms|Acute Pain|Chronic Pain|Dyspnea|Low Back Pain|Mucositis|Myocardial Infarction|Neoplasms|Pain|Pruritus|Pulmonary Disease, Chronic Obstructive|Scoliosis|Stomatitis|Substance-Related Disorders	33
mosunetuzumab	Lymphoma, Follicular	43
motixafortide	Multiple Myeloma	-
moxetumomab pasudotox	Leukemia, Hairy Cell|Neoplasms	19
mrtx-849	Carcinoma, Non-Small-Cell Lung	42
nabilone	Nausea|Neoplasms|Postoperative Nausea and Vomiting	-
Necitumumab	Carcinoma, Non-Small-Cell Lung|Neoplasms	-
Nelarabine	Precursor T-Cell Lymphoblastic Leukemia-Lymphoma	-
neratinib	Breast Neoplasms	85
neratinib maleate	Breast Neoplasms	-
Nilotinib	Leukemia|Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Leukemia, Myeloid	84
Nilutamide	Prostatic Neoplasms	14

niraparib	Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Peritoneal Neoplasms	30
Nivolumab	Melanoma	-
nogapendekin alfa	Urinary Bladder Neoplasms	44
Norepinephrine	Carcinoma|Carcinoma, Hepatocellular|Cardiovascular Diseases|Depressive Disorder|Hypotension|Hypotension, Orthostatic|Multiple System Atrophy|Poliomyelitis|Sepsis|Shock|Shock, Septic	3
Obinutuzumab	Leukemia, Lymphocytic, Chronic, B-Cell	-
Octreotide	Acromegaly|Carcinoid Tumor|Diarrhea|Neoplasms|Obesity|Vipoma	61
Ofatumumab	Leukemia, Lymphocytic, Chronic, B-Cell	-
Olaparib	Breast Neoplasms|Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Neoplasms|Ovarian Neoplasms|Pancreatic Neoplasms|Peritoneal Neoplasms|Prostatic Neoplasms, Castration-Resistant	46
olaratumab	Sarcoma	-
Ondansetron	Alcoholism|Breast Neoplasms|Gastroenteritis|Hypotension|Irritable Bowel Syndrome|Nausea|Neoplasms|Obsessive-Compulsive Disorder|Postoperative Nausea and Vomiting|Vomiting	4
Osimertinib	Carcinoma, Non-Small-Cell Lung|Lung Neoplasms|Neoplasms	89
Oxaliplatin	Colorectal Neoplasms|Liver Neoplasms	86
Oxycodone	Low Back Pain|Neoplasms|Pain|Substance-Related Disorders	-
Paclitaxel	Adenocarcinoma|Breast Neoplasms|Carcinoma, Non-Small-Cell Lung|Constriction, Pathologic|Coronary Restenosis|Ischemia|Neoplasms|Ovarian Neoplasms|Peripheral Arterial Disease|Peripheral Vascular Diseases	90
Palbociclib	Breast Neoplasms	48
palifosfamide	Neoplasms|Testicular Neoplasms	-
Palonosetron	Nausea|Neoplasms|Postoperative Nausea and Vomiting|Vomiting	-
Pamidronate	Bone Diseases|Breast Neoplasms|Hypercalcemia|Osteitis Deformans|Osteogenesis Imperfecta	30
Panitumumab	Colorectal Neoplasms	39
Panobinostat	Multiple Myeloma	80
Papaverine	Digestive System Diseases|Erectile Dysfunction|Kidney Neoplasms|Neoplasms	-
Paricalcitol	Diabetic Nephropathies|Hyperparathyroidism, Secondary|Kidney Diseases|Neoplasms|Renal Insufficiency, Chronic	35
Pazopanib	Carcinoma, Renal Cell|Sarcoma	91
pazopanib hydrochloride	Carcinoma, Renal Cell|Sarcoma	-
Pegaspargase	Precursor Cell Lymphoblastic Leukemia-Lymphoma	-
Pembrolizumab	Carcinoma, Hepatocellular|Carcinoma, Merkel Cell|Carcinoma, Non-Small-Cell Lung|Carcinoma, Renal Cell|Carcinoma, Transitional Cell|Hodgkin Disease|Melanoma|Neoplasms|Stomach Neoplasms	-
Pemetrexed	Carcinoma, Non-Small-Cell Lung|Lung Neoplasms|Mesothelioma|Neoplasms|Renal Insufficiency	-
pemigatinib	Cholangiocarcinoma|Neoplasms	81
Pentostatin	Leukemia, Hairy Cell	2
Pertuzumab	Breast Neoplasms	88
Pipobroman	Neoplasms	-
pirtobrutinib	Lymphoma, Mantle-Cell	-
Pixantrone	Neoplasms	61
Plerixafor	Lymphoma|Lymphoma, Non-Hodgkin|Multiple Myeloma	-
Podofilox	Carcinoma, Squamous Cell|Condylomata Acuminata|Virus Diseases	34
polatuzumab vedotin	Lymphoma, Large B-Cell, Diffuse|Neoplasms	-
Pomalidomide	Multiple Myeloma	31
Ponatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Precursor Cell Lymphoblastic Leukemia-Lymphoma	89
Porfimer	Esophageal Neoplasms	-
Posaconazole	Aspergillosis|Candidiasis|Leukemia|Leukemia, Myeloid, Acute|Mycoses|Neutropenia	-
Potassium Citrate	Acidosis, Renal Tubular|Kidney Calculi|Neoplasms|Stomach Neoplasms	-
Povidone-iodine	Breast Neoplasms|Surgical Wound|Surgical Wound Infection|Wound Infection|Wounds and Injuries	-
Pralatrexate	Lymphoma, T-Cell, Peripheral	-
pralsetinib	Carcinoma, Medullary|Carcinoma, Non-Small-Cell Lung	-
Prednicarbate	Adrenal Hyperplasia, Congenital|Anemia|Arthritis, Juvenile|Arthritis, Psoriatic|Arthritis, Rheumatoid|Brain Neoplasms|Bursitis|Conjunctivitis, Allergic|Dermatitis, Atopic|Endocrine System Diseases|Inflammation|Multiple Sclerosis|Neoplasms|Osteoarthritis|Peptic Ulcer|Rhinitis, Allergic|Skin Diseases|Spondylitis|Tenosynovitis|Uveitis, Posterior	9
Prednisolone	Addison Disease|Adrenal Hyperplasia, Congenital|Anemia|Anemia, Aplastic|Anemia, Hemolytic|Arthritis|Arthritis, Gouty|Arthritis, Juvenile|Arthritis, Psoriatic|Arthritis, Rheumatoid|Asthma|Berylliosis|Brain Neoplasms|Bursitis|Chorioretinitis|Choroiditis|Colitis, Ulcerative|Conjunctivitis, Allergic|Crohn Disease|Dermatitis Herpetiformis|Dermatitis, Atopic|Dermatitis, Contact|Dermatitis, Exfoliative|Dermatitis, Seborrheic|Dermatomyositis|Endocrine System Diseases|Erythema Multiforme|Eye Diseases|Hemorrhoids|Herpes Zoster Ophthalmicus|Hypercalcemia|Inflammation|Iridocyclitis|Iritis|Keratitis|Leukemia|Lung Diseases|Lupus Erythematosus, Systemic|Lupus Nephritis|Lymphoma|Multiple Sclerosis|Mycosis Fungoides|Myocarditis|Nasal Obstruction|Neoplasms|Nephrotic Syndrome|Ophthalmia, Sympathetic|Optic Neuritis|Osteoarthritis|Pain|Pemphigus|Peptic Ulcer|Pneumonia|Polymyositis|Psoriasis|Pulmonary Disease, Chronic Obstructive|Pulmonary Eosinophilia|Pulpitis|Purpura, Thrombocytopenic, Idiopathic|Rhinitis, Allergic|Rhinitis, Allergic, Seasonal|Sarcoidosis|Serum Sickness|Sinusitis|Skin Diseases|Spondylitis|Spondylitis, Ankylosing|Stevens-Johnson Syndrome|Synovitis|Tennis Elbow|Tenosynovitis|Thrombocytopenia|Thyroiditis, Subacute|Trichinellosis|Tuberculosis, Meningeal|Tuberculosis, Pulmonary|Uveitis|Uveitis, Posterior	43

prednisolone phosphoric acid	Anemia|Asthma|Conjunctivitis, Allergic|Corneal Injuries|Idiopathic Pulmonary Fibrosis|Inflammation|Leukemia|Multiple Sclerosis|Nephrotic Syndrome|Pulmonary Disease, Chronic Obstructive|Pulmonary Fibrosis|Rhinitis, Allergic|Uremia|Uveitis	21
Prednisone	Addison Disease|Adrenal Hyperplasia, Congenital|Anemia, Aplastic|Anemia, Hemolytic|Arthritis|Arthritis, Gouty|Arthritis, Juvenile|Arthritis, Psoriatic|Arthritis, Rheumatoid|Asthma|Berylliosis|Bursitis|Chorioretinitis|Choroiditis|Colitis, Ulcerative|Conjunctivitis, Allergic|Crohn Disease|Dermatitis Herpetiformis|Dermatitis, Atopic|Dermatitis, Contact|Dermatitis, Exfoliative|Dermatitis, Seborrheic|Dermatomyositis|Erythema Multiforme|Giant Cell Arteritis|Heart Failure|Hematologic Diseases|Herpes Zoster Ophthalmicus|Hypercalcemia|Hypereosinophilic Syndrome|Infections|Iridocyclitis|Iritis|Keratitis|Leukemia|Lung Diseases|Lupus Erythematosus, Systemic|Lymphoma|Multiple Sclerosis|Mycosis Fungoides|Myocarditis|Nephrotic Syndrome|Ophthalmia, Sympathetic|Optic Neuritis|Osteoarthritis|Pemphigus|Pneumonia|Polymyalgia Rheumatica|Polymyositis|Psoriasis|Pulmonary Disease, Chronic Obstructive|Pulmonary Eosinophilia|Purpura, Thrombocytopenic, Idiopathic|Respiratory Tract Infections|Rhinitis, Allergic, Seasonal|Sarcoidosis|Serum Sickness|Spondylitis, Ankylosing|Stevens-Johnson Syndrome|Synovitis|Tennis Elbow|Tenosynovitis|Thrombocytopenia|Thyroiditis, Subacute|Trichinellosis|Tuberculosis, Meningeal|Tuberculosis, Pulmonary|Uveitis, Posterior|Vestibular Neuronitis	12
Procarbazine	Neoplasms	24
Progesterone	Amenorrhea|Endometrial Hyperplasia|Hemorrhage|Infertility|Premature Birth|Uterine Hemorrhage	80
Propofol	Breast Neoplasms|Coronary Artery Disease|Heart Diseases|Inflammation|Neoplasms|Obesity, Morbid|Psychomotor Agitation|Respiratory Insufficiency|Scoliosis|Wounds and Injuries	30
Quetiapine	Alcoholism|Anxiety|Bipolar Disorder|Cocaine-Related Disorders|Colitis-Associated Neoplasms|Delirium|Dementia|Depressive Disorder|Depressive Disorder, Major|Mental Disorders|Mood Disorders|Obsessive-Compulsive Disorder|Parkinson Disease|Phobia, Social|Psychomotor Agitation|Psychotic Disorders|Schizophrenia|Sleep Initiation and Maintenance Disorders|Stress Disorders, Post-Traumatic	-
quizartinib	Leukemia, Myeloid, Acute	85
Radium Ra 223 Dichloride	Neoplasm Metastasis|Prostatic Neoplasms|Prostatic Neoplasms, Castration-Resistant	-
Raloxifene	Breast Neoplasms|Osteoporosis|Osteoporosis, Postmenopausal|Psychotic Disorders|Schizophrenia	55
Raltitrexed	Neoplasms	34
Ramucirumab	Stomach Neoplasms	-
Rasburicase	Leukemia|Lymphoma|Neoplasms	-
Regorafenib	Colorectal Neoplasms	96
relugolix	Prostatic Neoplasms	-
Remifentanil	Hypotension|Neoplasms|Respiratory Insufficiency	-
repotrectinib	Carcinoma, Non-Small-Cell Lung	22
retifanlimab	Carcinoma, Merkel Cell	22
Ribavirin	Fibrosis|Hepatitis|Hepatitis C|Hepatitis C, Chronic|HIV Infections|Infections|Kidney Diseases|Liver Cirrhosis|Neoplasms|Renal Insufficiency|Renal Insufficiency, Chronic|Respiratory Syncytial Virus Infections|Virus Diseases	38
ribociclib	Breast Neoplasms	62
ripretinib	Gastrointestinal Stromal Tumors|Neoplasms	86
Risperidone	Aggression|Alzheimer Disease|Anxiety|Attention Deficit and Disruptive Behavior Disorders|Autistic Disorder|Bipolar Disorder|Child Development Disorders, Pervasive|Colitis-Associated Neoplasms|Dementia|Developmental Disabilities|Psychotic Disorders|Schizophrenia|Stress Disorders, Post-Traumatic	-
Rituximab	Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis|Lymphoma, B-Cell|Lymphoma, Follicular|Vasculitis	25
rivoceranib mesylate	Lymphoma|Neoplasms|Ovarian Neoplasms|Stomach Neoplasms	-
Romidepsin	Lymphoma, T-Cell, Cutaneous	85
Ropivacaine	Acute Pain|Appendicitis|Breast Neoplasms|Fractures, Bone|Hallux Valgus|Joint Diseases|Muscle Weakness|Neoplasms|Osteoarthritis|Osteoarthritis, Knee|Pain|Paralysis|Paresis|Rotator Cuff Injuries	-
Rosuvastatin	Acute Coronary Syndrome|Atherosclerosis|Cardiovascular Diseases|Coronary Artery Disease|Coronary Disease|Diabetes Mellitus|Diabetes Mellitus, Type 2|Dyslipidemias|Heart Failure|HIV Infections|Hypercholesterolemia|Hyperlipidemia, Familial Combined|Hyperlipidemias|Hyperlipoproteinemia Type II|Hyperlipoproteinemia Type IV|Hypertension|Hypertriglyceridemia|Internal Hernia|Ischemia|Metabolic Diseases|Neoplasms|Periodontitis|Prostatic Neoplasms|Renal Insufficiency|Stroke	-
rucaparib	Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Peritoneal Neoplasms|Prostatic Neoplasms, Castration-Resistant	76
sacituzumab govitecan	Breast Neoplasms|Triple Negative Breast Neoplasms	-
Salicylic acid	Acne Vulgaris|Callosities|Dandruff|Dermatitis, Seborrheic|Eye Diseases|Fever|Inflammation|Melanosis|Pain|Pruritus|Psoriasis|Skin Diseases|Skin Neoplasms|Sunburn|Warts	18
Sargramostim	COVID-19|Leukemia, Myeloid, Acute	68
selinexor	Multiple Myeloma	73
selpercatinib	Carcinoma, Medullary|Carcinoma, Non-Small-Cell Lung|Lung Neoplasms|Thyroid Neoplasms	82
Sildenafil	Diabetes Mellitus|Emphysema|Erectile Dysfunction|Familial Primary Pulmonary Hypertension|Heart Diseases|Heart Failure|Hypertension|Hypertension, Pulmonary|Lung Diseases|Parkinson Disease|Persistent Fetal Circulation Syndrome|Prostatic Hyperplasia|Pulmonary Arterial Hypertension|Pulmonary Edema	-
Silodosin	Prostatic Hyperplasia	-
Siltuximab	Giant Lymph Node Hyperplasia	-
Sodium Chloride	Acid-Base Imbalance|Cerebral Palsy|Common Cold|Corneal Edema|Diabetes Mellitus|Dry Eye Syndromes|Electrolytes|Eye Diseases|Fractures, Bone|Graves Ophthalmopathy|Heart Failure|Hemorrhage|Hypothermia|Kidney Diseases|Muscle	62

	Spasticity|Neoplasms|Osteoarthritis|Osteoarthritis, Knee|Paralysis|Renal Insufficiency|Tennis Elbow|Wounds and Injuries	
Solifenacin	Prostatic Hyperplasia|Urinary Bladder, Overactive|Urinary Incontinence|Urinary Incontinence, Urge	-
Sonidegib	Carcinoma, Basal Cell	9
Sorafenib	Carcinoma|Carcinoma, Hepatocellular|Carcinoma, Renal Cell|Thyroid Neoplasms	96
sotorasib	Carcinoma, Non-Small-Cell Lung	42
Strontium chloride Sr-89	Neoplasm Metastasis	-
Sugammadex	Hypothermia|Neoplasms|Postoperative Complications	-
Sunitinib	Adenoma, Islet Cell|Carcinoma|Carcinoma, Renal Cell|Gastrointestinal Stromal Tumors|Neoplasms|Neuroendocrine Tumors	97
Tadalafil	Diabetes Mellitus, Type 2|Erectile Dysfunction|Hypertension|Hypertension, Pulmonary|Insulin Resistance|Lower Urinary Tract Symptoms|Muscular Dystrophies|Muscular Dystrophy, Duchenne|Prostatic Hyperplasia|Pulmonary Arterial Hypertension|Scleroderma, Systemic	-
tafasitamab	Lymphoma|Lymphoma, Large B-Cell, Diffuse|Neoplasms	-
talazoparib	Breast Neoplasms	56
talquetamab	Multiple Myeloma	43
Tamoxifen	Adenoma|Breast Neoplasms|Neoplasms	84
Tamsulosin	Hyperplasia|Nocturia|Prostatic Hyperplasia|Ureterolithiasis|Urinary Retention|Urination Disorders	-
tarlatamab	Small Cell Lung Carcinoma	43
tazemetostat	Lymphoma, Follicular|Sarcoma	38
tebentafusp	Uveal Neoplasms	-
teclistamab	Multiple Myeloma	43
Tegafur	Neoplasms	90
Temozolomide	Astrocytoma|Brain Neoplasms|Central Nervous System Neoplasms|Glioblastoma|Neoplasms	19
Temsirolimus	Carcinoma, Renal Cell|Lymphoma|Lymphoma, Mantle-Cell|Lymphoma, Non-Hodgkin	87
Teniposide	Precursor Cell Lymphoblastic Leukemia-Lymphoma	80
tepotinib	Carcinoma, Non-Small-Cell Lung|Neoplasms	82
Terazosin	Hypertension|Prostatic Hyperplasia	24
Testosterone	Brain Injuries|Brain Injuries, Traumatic|Erectile Dysfunction|Hypogonadism|Insulin Resistance|Klinefelter Syndrome|Neoplasms|Obesity|Orchitis|Sarcopenia|Wounds and Injuries	72
testosterone cypionate	Hypogonadism|Neoplasms|Orchitis	-
testosterone undecanoate	Hypogonadism|Klinefelter Syndrome|Neoplasms|Orchitis	35
Thalidomide	Immune System Diseases|Multiple Myeloma|Neoplasms	81
Thiotepa	Adenocarcinoma|Carcinoma|Hodgkin Disease|Neoplasms	51
thyrotropin alfa	Thyroid Neoplasms	-
Tioguanine	Neoplasms	25
Tipiracil	Colorectal Neoplasms	-
tirabrutinib	Lymphoma	-
tisagenlecleucel	Neoplasms	-
tislelizumab	Esophageal Squamous Cell Carcinoma	25
tisotumab vedotin	Uterine Cervical Neoplasms	-
tivozanib	Carcinoma, Renal Cell	86
Topotecan	Small Cell Lung Carcinoma	54
Toremifene	Breast Neoplasms|Neoplasms	73
toripalimab	Nasopharyngeal Carcinoma	22
Tositumomab	Lymphoma, Follicular	27
Trabectedin	Leiomyosarcoma|Liposarcoma	-
Trametinib	Carcinoma, Non-Small-Cell Lung|Melanoma	90
Tranexamic Acid	Blood Coagulation Disorders|Epistaxis|Femoral Neck Fractures|Fractures, Bone|Gastrointestinal Hemorrhage|Hematoma|Hematoma, Subdural|Hematoma, Subdural, Chronic|Hemophilia A|Hemorrhage|Hip Fractures|Joint Diseases|Menorrhagia|Neoplasms|Osteoarthritis|Osteoarthritis, Knee|Placenta Accreta|Placenta Previa|Postpartum Hemorrhage|Wounds and Injuries	-
Trastuzumab	Breast Neoplasms	81
trastuzumab deruxtecan	Breast Neoplasms|Neoplasms	79
tremelimumab	Carcinoma, Hepatocellular	39
treosulfan	Neoplasms	-
Triclosan	Breast Neoplasms|Gingivitis|Periodontal Diseases|Periodontitis	89
Trifluridine	Colorectal Neoplasms|Eye Infections|Herpes Simplex|Keratoconjunctivitis|Neoplasms	-
trilaciclib	Small Cell Lung Carcinoma	56
Triptorelin	Endometriosis|Infertility|Neoplasms|Prostatic Neoplasms	82
tucatinib	Breast Neoplasms	86
umbralisib	Lymphoma, B-Cell, Marginal Zone|Lymphoma, Follicular	74
Uracil mustard	Neoplasms	-
Valganciclovir	Acquired Immunodeficiency Syndrome|Cytomegalovirus Infections|Cytomegalovirus Retinitis|Infections|Leukemia, Lymphocytic, Chronic, B-Cell|Retinitis|Virus Diseases	-
Valproic Acid	Alzheimer Disease|Anorexia|Autistic Disorder|Bipolar Disorder|Colitis-Associated Neoplasms|Depressive Disorder|Depressive Disorder, Major|Epilepsy|Epilepsy, Absence|Epilepsy, Complex Partial|Migraine Disorders|Mitochondrial Diseases|Mood Disorders|Schizophrenia|Seizures|Vomiting	83
Valrubicin	Urinary Bladder Neoplasms	61
Vandetanib	Thyroid Neoplasms	93
Vemurafenib	Melanoma|Neoplasms	78
venetoclax	Leukemia, Lymphocytic, Chronic, B-Cell|Leukemia, Myeloid, Acute	52

Vincristine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	47
vincristine	Neoplasms	-
vinflunine	Neoplasms	-
Vinorelbine	Breast Neoplasms|Carcinoma, Non-Small-Cell Lung|Lung Neoplasms|Neoplasms	57
vipivotide tetraxetan lutetium lu-177	Prostatic Neoplasms, Castration-Resistant	29
Vismodegib	Carcinoma|Carcinoma, Basal Cell	13
Vorinostat	Lymphoma, T-Cell, Cutaneous	85
zanubrutinib	Lymphoma, Mantle-Cell	78
Ziprasidone	Anxiety|Bipolar Disorder|Colitis-Associated Neoplasms|Depressive Disorder|Depressive Disorder, Major|Mood Disorders|Psychotic Disorders|Schizophrenia	-
Zoledronate	Bone Diseases|Bone Diseases, Metabolic|Bone Neoplasms|Breast Neoplasms|Carcinoma, Non-Small-Cell Lung|Carcinoma, Renal Cell|Multiple Myeloma|Neoplasm Metastasis|Osteitis Deformans|Osteoarthritis, Hip|Osteoporosis|Osteoporosis, Postmenopausal|Pain|Prostatic Neoplasms|Spinal Cord Injuries	5

6. Conclusion

We applied the software package "Genome Enhancer" to a data set that contains *genomics* data. The study is done in the context of *Colorectal Neoplasms*. The data were pre-processed, statistically analyzed and genes carrying sequence variations were identified. Also checked was the enrichment of GO or disease categories among the studied gene sets.

We propose the following drugs as most promising candidates for treating the pathology under study:

Sunitinib, seliciclib, LE-SN38 and 2,6-Dihydroanthra/1,9-Cd/Pyrazol-6-One

These drugs were selected for acting on the following targets: INSR, HIF1A and AKT2, which were predicted to be involved in the molecular mechanism of the pathology under study.

The identified molecular mechanism of the studied pathology was predicted to be mainly based on the following key drug targets:

Ubc9(h):sumo3, PKCzeta, IRF-1, InsR and Ubc9:sumo3

These potential drug targets should be considered as a prospective research initiative for further drug repurposing and drug development purposes. The following drugs were predicted as, matching those drug targets: Fadraciclib, Sunitinib, Sorafenib, Uracil mustard, seliciclib and Rbt205 Inhibitor. These drugs should be considered with special caution for research purposes only.

In this study, we came up with a detailed signal transduction network regulating genes carrying sequence variations in the studied pathology. In this network we have revealed the following top master regulators (signaling proteins and their complexes) that play a crucial role in the molecular mechanism of the studied pathology, which can be proposed as the most promising molecular targets for further drug repurposing and drug development initiatives.

- Ubc9(h):sumo3
- PKCzeta
- IRF-1
- InsR
- Ubc9:sumo3

Potential drug compounds which can be affecting these targets can be found in the "Finding prospective drug targets" section.

7. Methods

Databases used in the study

Transcription factor binding sites in promoters and enhancers of genes carrying sequence variations were analyzed using known DNA-binding motifs described in the TRANSFAC® library, release 2025.1 (geneXplain GmbH, Wolfenbüttel, Germany) (https://genexplain.com/transfac).
The master regulator search uses the TRANSPATH® database (BIOBASE), release 2025.1 (geneXplain GmbH, Wolfenbüttel, Germany) (https://genexplain.com/transpath). A comprehensive signal transduction network of human cells is built by the software on the basis of reactions annotated in TRANSPATH®.
The information about drugs corresponding to identified drug targets and clinical trials references were extracted from HumanPSD™ database, release 2025.1 (https://genexplain.com/humanpsd).
The Ensembl database release Human112.38 (hg38) (http://www.ensembl.org) was used for gene IDs representation and Gene Ontology (GO) (http://geneontology.org) was used for functional classification of the studied gene set.

Genomic data processing

When analyzing a list of genomic variations (from input vcf file or computed by Genome Enhancer from SNP list or from fastq files), first of all, we compute a specific mutation weight (w_1) for each variation depending on it's location in gene body and gene flanking regions (-1000 upstream and +1000 downstream of the gene body).

w_1 = 0.7 for variations in exon area
w_1 = 1.3 for variations in promoter region (-1000bp upstream and 100bp downstream of TSS),
w_1 = 1.0 for variations in other locations.

Next, VCF track (Yes track), provided as input or created by Genome Enhancer from SNP list or fastq files, is compared to Random VCF track (No track) of 10000 random human variations. On both tracks we calculate the score delta values (differences between PWM score values of the TF sites with the reference or with the alternative allele of the considered variation). For each variation we find then the maximal score delta values at each PWM leading either to the gain or to the loss of TF site (with the alternative allele). For selecting the maximum score delta values we consider both directions of DNA strand. Next, by going through all variations we compute two p-values for each PWM – the p-value of site losses and p-value of site gains. The p-values are computed using cumulative Binomial distribution estimating the random chances to observe the found high number of lost or gained TF sites in Yes track in the comparison to the No track. The PWM cut-offs are optimized to obtain the most extreme p-values. We further take top 20 best matrices by p-value from each: gained and lost sites and calculate the mutation weights on the Yes track on the basis of the obtained 40 matrices. Each mutation is assigned with a respective matrix that got the maximum delta value either for the site gain or for the site loss (changed the binding affinity most significantly). This delta is then compared to other delta values that were computed for the respective matrix on the No track. The eventual weight that reflects the transcription factor binding affinity change caused by the mutation is calculated as follows:

w_2 = -log10(NoGr / NoAll), if NoGr > 0
w_2 = -log10(1.0 / (2.0 * NoAll), if NoGr = 0

where NoGr is the number of deltas from the No track that appeared to be greater than the inspected delta and NoAll is the total number of deltas in the No track. The resulting track is then constructed that contains all sites of the initial Yes track together with the additional weights reflecting the transcription factor binding affinity change caused by the mutation.
The list of 40 matrices most affected by variations will be further used in composite modules search described in the next section.
Total Gene mutation weight is the sum of the weights w_1 of all variations located inside the gene body and in the gene flanking regions summed up with the weight w_2 that reflects the transcription factor binding affinity change caused by the mutation. This weight is calculated by estimating the importance of a certain mutation in terms of gains or losses of binding sites caused by it.
Next, a weighted score is calculated for all genes with the following formula:
Weighted score = In_disease * In_transpath * Gene mutation weight, where

In_disease = 2.0 for genes assigned to selected diseases,
In_transpath = 1.5 for genes mapped to Transpath pathways,
and In_disease = In_transpath = 1.0 in all other cases.

At the next step, 300 genes with highest weighted score are selected for further CMA model search.
The mutation weights ($w = w_1+w_2$) are also used to find the regulatory regions of the genes most affected by the variations/SNP. A sliding window of 1100 bp is used to scan through the intronic, 5' and 3' regions of the genes and a region is selected with the highest sum of the mutation weights.

Methods for the analysis of enriched transcription factor binding sites and composite modules

Transcription factor binding sites in promoters and enhancers of differentially expressed genes were analyzed using known DNA-binding motifs. The motifs are specified using position weight matrices (PWMs) that give weights to each nucleotide in each position of the DNA binding motif for a transcription factor or a group of them.
We search for transcription factor binding sites (TFBS) that are enriched in the enhancers under study as compared to a background set of promoters of housekeeping genes. We denote study and background sets briefly as Yes and No sets. In the current work we used a workflow considering promoter sequences of a standard length of 1100 bp (-1000 to +100). The error rate in this part of the pipeline is controlled by estimating the adjusted p-value (using the Benjamini-Hochberg procedure) in comparison to the TFBS frequency found in randomly selected regions of the human genome (adj.p-value < 0.01).
We have applied the CMA algorithm (Composite Module Analyst) for searching composite modules [6] in the promoters and enhancers of the Yes and No sets. We searched for a composite module consisting of a cluster of 10 TFs in a sliding window of 200-300 bp that statistically significantly separates sequences in the Yes and No sets (minimizing Wilcoxon p-value). Each composite module is forced to include at least one matrix that was identified as matrix causing the significant change in the transcription factor binding affinity as the result of the observed mutation.

Methods for finding master regulators in networks

We searched for master regulator molecules in signal transduction pathways upstream of the identified transcription factors. The master regulator search uses a comprehensive signal transduction network of human cells. The main algorithm of the master regulator search has been described earlier [3,4]. The goal of the algorithm is to find nodes in the global signal transduction network that may potentially regulate the activity of a set of transcription factors found at the previous step of the analysis. Such nodes are considered as most promising drug targets, since any influence on such a node may switch the transcriptional programs of hundreds of genes that are regulated by the respective TFs. In our analysis, we have run the algorithm with a maximum radius of 12 steps upstream of each TF in the input set. The error rate of this algorithm is controlled by applying it 10000 times to randomly generated sets of input transcription factors of the same set-size. Z-score and FDR value of ranks are calculated then for each potential master regulator node on the basis of such random runs (see detailed description in [8]). We control the error rate by the FDR threshold 0.05.
To identify feed forward loops in transduction network we calculate regulatory scores for transcription factors from CMA result and keynodes analysis. The matrices from the CMA model are converted to TFs. Keynode analysis is then performed on these TFs and resulting keynodes are sorted by keynode score. Then the keynodes, which are

$$S_j = \sum_{j=1}^{M_j} \frac{1}{D_{i,j}}; \; D_{i,j} = \sum_{k=1}^{C_{i,j}} d_k$$

regulated by the model, are selected.
Here:

- j – a TF (Transcription Factor),
- i – a MR (Master Regulator),
- S_j – Regulatory score of the TF,
- $D_{i,j}$– Cumulative distance between MR i and TF j,
- M_j – number of MRs whose signal can reach the TF j and whose gene is regulated by TF j,
- $C_{i,j}$ – number of steps in the network from between MR i and TF j (shortest path),
- $d_k$distance of the step k in the shortest path between MR i and TF j.

In unweighted TRANSPATH network $d_k = 1$ for each direct signaling reaction (like A+B-C = D), $d_k >= 3$ for each semantic reaction (like A → B). It depends on type of the reaction, basic or orthology level of it's components, species of the components.
In weighted TRANSPATH network d_k is changed after applying the Context Algorithm as described in [4].

Methods for analysis of pharmaceutical compounds

We seek for the optimal combination of molecular targets (key elements of the regulatory network of the cell) that potentially interact with pharmaceutical compounds from a library of known drugs and biologically active chemical compounds, using information about known drugs from HumanPSD™ and predicting potential drugs using PASS program.

Method for analysis of known pharmaceutical compounds

We selected compounds from HumanPSD™ database that have at least one target. Next, we sort compounds using "*Drug rank*" that is the sum of the following ranks:

1. ranking by "Target activity score" (*T-score$_{PSD}$*),
2. ranking by "Disease activity score" (*D-score$_{PSD}$*),
3. ranking by "Clinical validity score".

"Target activity score" (*T-score$_{PSD}$*) is calculated as follows:

$$T\text{-}score_{PSD} = -\frac{|T|}{|T| + w(|AT| - |T|))} \sum_{t \in T} log_{10}\left(\frac{rank(t)}{1 + maxRank(T)}\right),$$

where *T* is set of all targets related to the compound intersected with input list, *|T|* is number of elements in *T*, *AT* and *|AT|* are set set of all targets related to the compound and number of elements in it, *w* is weight multiplier, *rank(t)* is rank of given target, *maxRank(T)* equals *max(rank(t))* for all targets *t* in *T*.
We use following formula to calculate "Disease activity score" (*D-score$_{PSD}$*):

$$D\text{-}score_{PSD} = \begin{cases} \sum\limits_{d \in D} \sum\limits_{p \in P} phase(d,p) \\ 0, \ D = \varnothing \end{cases},$$

where *D* is the set of selected diseases, and if *D* is empty set, *D-score$_{PSD}$=0*. *P* is a set of all known phases for each disease, *phase(p,d)* equals to the phase number if there are known clinical trials for the selected disease on this phase and zero otherwise.
The clinical validity score reflects the number of the highest clinical trials phase (from 1 to 4) on which the drug was ever tested for any pathology.

Method for prediction of pharmaceutical compounds

In this study, the focus was put on compounds with high pharmacological efficiency and low toxicity. For this purpose, comprehensive library of chemical compounds and drugs was subjected to a SAR/QSAR analysis. This library contains 13040 compounds along with their pre-calculated potential pharmacological activities of those substances, their possible side and toxic effects, as well as the possible mechanisms of action. All biological activities are expressed as probability values for a substance to exert this activity (*Pa*).
We selected compounds that satisfied the following conditions:

1. Toxicity below a chosen toxicity threshold (defines as *Pa*, probability to be active as toxic substance).
2. For all predicted pharmacological effects that correspond to a set of user selected disease(s) *Pa* is greater than a chosen effect threshold.
3. There are at least 2 targets (corresponding to the predicted activity-mechanisms) with predicted *Pa* greater than a chosen target threshold.

The maximum *Pa* value for all toxicities corresponding to the given compound is selected as the "Toxicity score". The maximum *Pa* value for all activities corresponding to the selected diseases for the given compound is used as the "Disease activity score". "Target activity score" (T-score) is calculated as follows:

$$T\text{-}score(s) = \frac{|T|}{|T| + w(|AT| - |T|))} \sum_{m \in M(s)} \left(pa(m) \sum_{g \in G(m)} IAP(g) optWeight(g) \right),$$

where *M(s)* is the set of activity-mechanisms for the given structure (which passed the chosen threshold for activity-mechanisms *Pa*); *G(m)* is the set of targets (converted to genes) that corresponds to the given activity-mechanism (m) for the given compound; *pa(m)* is the probability to be active of the activity-mechanism (m), *IAP(g)* is the invariant accuracy of prediction for gene from *G(m)*; *optWeight(g)* is the additional weight multiplier for gene. *T* is set of all targets related to the compound intersected with input list, *|T|* is number of elements in *T*, *AT* and *|AT|* are set set of all targets related to the compound and number of elements in it, *w* is weight multiplier.
"Druggability score" (D-score) is calculated as follows:

$$D\text{-}score(g) = IAP(g) \sum_{s \in S(g)} \sum_{m \in M(s,g)} pa(m),$$

where *S(g)* is the set of structures for which target list contains given target, *M(s,g)* is the set of activity-mechanisms (for the given structure) that corresponds to the given gene, *pa(m)* is the probability to be active of the activity-mechanism (m), *IAP(g)* is the invariant accuracy of prediction for the given gene.

8. References

1. Kel A, Voss N, Jauregui R, Kel-Margoulis O, Wingender E. Beyond microarrays: Finding key transcription factors controlling signal transduction pathways. *BMC Bioinformatics.* **2006**;7(S2), S13. doi:10.1186/1471-2105-7-s2-s13
2. Stegmaier P, Voss N, Meier T, Kel A, Wingender E, Borlak J. Advanced Computational Biology Methods Identify Molecular Switches for Malignancy in an EGF Mouse Model of Liver Cancer. *PLoS ONE.* **2011**;6(3):e17738. doi:10.1371/journal.pone.0017738
3. Koschmann J, Bhar A, Stegmaier P, Kel A, Wingender E. "Upstream Analysis": An Integrated Promoter-Pathway Analysis Approach to Causal Interpretation of Microarray Data. *Microarrays.* **2015**;4(2):270-286. doi:10.3390/microarrays4020270.
4. Kel A, Stegmaier P, Valeev T, Koschmann J, Poroikov V, Kel-Margoulis OV, and Wingender E. Multi-omics "upstream analysis" of regulatory genomic regions helps identifying targets against methotrexate resistance of colon cancer. *EuPA Open Proteom.* **2016**;13:1-13. doi:10.1016/j.euprot.2016.09.002
5. Matys V, Kel-Margoulis OV, Fricke E, Liebich I, Land S, Barre-Dirrie A, Reuter I, Chekmenev D, Krull M, Hornischer K, Voss N, Stegmaier P, Lewicki-Potapov B, Saxel H, Kel AE, Wingender E. TRANSFAC and its module TRANSCompel: transcriptional gene regulation in eukaryotes. *Nucleic Acids Res.* **2006**;34(90001):D108-D110. doi:10.1093/nar/gkj143
6. Kel AE, Gössling E, Reuter I, Cheremushkin E, Kel-Margoulis OV, Wingender E. MATCH: A tool for searching transcription factor binding sites in DNA sequences. *Nucleic Acids Res.* **2003**;31(13):3576-3579. doi:10.1093/nar/gkg585
7. Waleev T, Shtokalo D, Konovalova T, Voss N, Cheremushkin E, Stegmaier P, Kel-Margoulis O, Wingender E, Kel A. Composite Module Analyst: identification of transcription factor binding site combinations using genetic algorithm. *Nucleic Acids Res.* **2006**;34(Web Server issue):W541-5.
8. Krull M, Pistor S, Voss N, Kel A, Reuter I, Kronenberg D, Michael H, Schwarzer K, Potapov A, Choi C, Kel-Margoulis O, Wingender E. TRANSPATH: an information resource for storing and visualizing signaling pathways and their pathological aberrations. *Nucleic Acids Res.* **2006**;34(90001):D546-D551. doi:10.1093/nar/gkj107
9. Boyarskikh U, Pintus S, Mandrik N, Stelmashenko D, Kiselev I, Evshin I, Sharipov R, Stegmaier P, Kolpakov F, Filipenko M, Kel A. Computational master-regulator search reveals mTOR and PI3K pathways responsible for low sensitivity of NCI-H292 and A427 lung cancer cell lines to cytotoxic action of p53 activator Nutlin-3. *BMC Med Genomics.* **2018**;11(1):12. doi:10.1186/1471-2105-7-s2-s13
10. Kel, A., Boyarskikh, U., Stegmaier, P., Leskov, L.S., Sokolov, A.V., Yevshin, I., Mandrik, N., Stelmashenko, D., Koschmann, J., Kel-Margoulis, O. and Krull, M. Walking pathways with positive feedback loops reveal DNA methylation biomarkers of colorectal cancer. *BMC bioinformatics.* Cambridge (UK): RSC Publishing. **2019**;20(Suppl 4):119:1-20. doi:10.1186/s12859-019-2687-7
11. Michael H, Hogan J, Kel A et al. Building a knowledge base for systems pathology. *Brief Bioinformatics.* **2008**;9(6):518-531. doi:10.1093/bib/bbn038
12. Filimonov D, Poroikov V. Probabilistic Approaches in Activity Prediction. Varnek A, Tropsha A. *Cheminformatics Approaches to Virtual Screening.* Cambridge (UK): RSC Publishing. **2008**;:182-216.

13. Filimonov DA, Poroikov VV. Prognosis of specters of biological activity of organic molecules. *Russian chemical journal*. **2006**;50(2):66-75 (russ)
14. Filimonov D, Poroikov V, Borodina Y, Gloriozova T. Chemical Similarity Assessment Through Multilevel Neighborhoods of Atoms: Definition and Comparison with the Other Descriptors. *ChemInform*. **1999**;39(4):666-670. doi:10.1021/ci980335o

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Supplementary material

1. Supplementary table 1 - Detailed report. Composite modules and master regulators (the most frequently mutated genes in Experiment: short-term survival).
2. Supplementary table 2 - Detailed report. Pharmaceutical compounds and drug targets.

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Decisions regarding care and treatment of patients should be fully made by attending doctors. The predicted chemical compounds listed in the report are given only for doctor's consideration and they cannot be treated as prescribed medication. It is the physician's responsibility to independently decide whether any, none or all of the predicted compounds can be used solely or in combination for patient treatment purposes, taking into account all applicable information regarding FDA prescribing recommendations for any therapeutic and the patient's condition, including, but not limited to, the patient's and family's medical history, physical examinations, information from various diagnostic tests, and patient preferences in accordance with the current standard of care. Whether or not a particular patient will benefit from a selected therapy is based on many factors and can vary significantly.

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