

The CDGnet tool consists of an evidence-based network approach for recommending targeted cancer therapies. It is currently hosted at <http://epiviz.cbcb.umd.edu/shiny/CDGnet/>, with the code being available at <https://github.com/SiminaB/CDGnet>. A preprint describing it within the scientific context is available at <https://www.biorxiv.org/content/10.1101/605261v1>. Its goal is to **prioritize targeted therapy assigned for cancer patients using drug-gene networks**. These networks include information from biological pathways, specially by looking at targets downstream of oncogenes (genes which are constitutively activated in cancer.) This is because once an oncogene is activated, it may only make sense to target and block genes and proteins that are found downstream of it, as upstream targeting may be ineffective.

Please note that this tool is for research purposes only. It is not intended for clinical care.

1) Necessary inputs

The assumption for users of this tool is that they will have:

- a **file with the molecular alterations** found in an individual tumor
- the individual's **cancer type** (currently restricted to cancer types that have existing KEGG pathways).

Users may either use the example molecular profile or input their own tsv or csv file with the same column headings. The landing page for CDGnet is shown below, with the example/allowable input format highlighted:

Therapy recommendations using biological networks

Warning! The following tool is for research purposes only. It is not intended for clinical care.

Select cancer type

Colorectal cancer

Input tsv or csv file with molecular alterations

Browse... No file selected

If a file is not uploaded, an example profile is loaded into the app.

Gene_protein	Data_type	Alteration
KRAS	mutation	G13V
PIK3CA	mutation	G1049S
BRCA2	mutation	deleterious

Filter Recommended Therapies

☒ Same Cancer Type

☒ Same Alteration

☒ FDA Approved Drugs

☒ FDA Approved Targeted Cancer Drugs

Category 1: FDA-approved drugs for which alterations in these genes/proteins are approved biomarkers in this tumor type:

Show 10 entries

Search:

Note

1 There are no recommended therapies in this category.

Showing 1 to 1 of 1 entries

Previous 1 Next

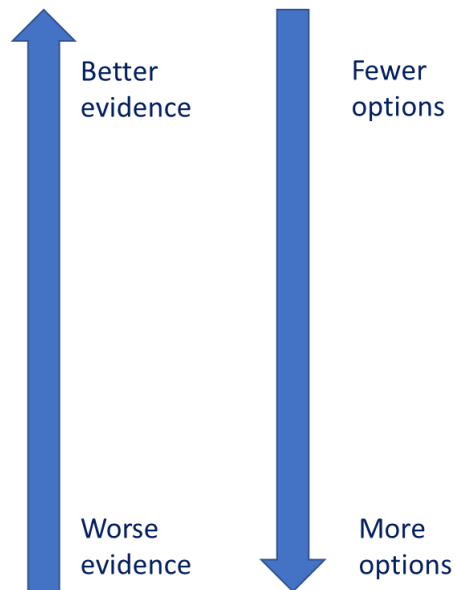
Allowable input format

We also provide an example for a tumor that is ER+ and has overexpression of FGFR1 (both csv and tsv files) at <https://github.com/SiminaB/CDGnet/tree/master/data>; this example is also used in the preprint for a putative breast cancer patient. After deciding to use the example profile or loading a data file, users also need to select a cancer type if it is something besides the default “Colorectal cancer.”

2) Categories of therapies for a patient with a given molecular profile

CDGnet provides 4 categories of targeted therapies:

1. FDA-approved drugs for which the patient's alterations/genes/proteins are biomarkers **in their tumor type**
2. FDA-approved drugs for which the patient's alterations/genes/proteins are biomarkers **in other tumor types**
3. Drugs which have as targets these alterations/genes/proteins or as biomarkers/targets others that **are downstream of input oncogenes** when considering **the pathway corresponding to this tumor type**.*
4. Drugs which have as targets/biomarkers either these alterations/genes/proteins or as biomarkers/targets others that **are downstream of input oncogenes** when considering **the pathways corresponding to other tumor types**.*



* Could be targeted drugs prescribed for their tumor type or other tumor types OR any FDA-approved drug OR any drug in DrugBank.

From category 1 to 4, the quality of evidence decreases, but the number of options decreases. Thus, category 1 therapies provide the highest level of evidence as they consist of FDA-approved therapies for which one or more of the alterations represent approved biomarkers. However, if there are no category 1 therapies, it may be necessary to move to the next categories.

3) Choosing therapy categories within the CDGnet tool

Each of these 4 categories corresponds to a combination of the first 2 checkboxes in the CDGnet webtool:

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PIK3CA	mutation	G1049S
BRCA2	mutation	deleterious

Filter Recommended Therapies

☒ Same Cancer Type ☒ Same Alteration → Category 1 therapies

☐ Same Cancer Type ☒ Same Alteration → Category 2 therapies

☒ Same Cancer Type ☐ Same Alteration → Category 3 therapies

☐ Same Cancer Type ☐ Same Alteration → Category 4 therapies

Category 1: FDA-approved drugs for which alterations in these genes/proteins are approved biomarkers in this tumor type:

Show: 10 entries

Note

1 There are no recommended therapies in this category.

Showing 1 to 1 of 1 entries

Previous 1 Next

Additionally, for Categories 3 and 4, users may choose to display only FDA-approved drugs or only FDA-approved targeted cancer drugs vs. all drugs in DrugBank:

Therapy recommendations using biological networks

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Colorectal cancer

Input tsv or csv file with molecular alterations
Browse... No file selected

If a file is not uploaded, an example profile is loaded into the app.

Gene_protein	Data_type	Alteration
KRAS	mutation	G13V
PIK3CA	mutation	G1049S
BRCA2	mutation	deleterious

Filter Recommended Therapies

- ☒ Same Cancer Type
- ☒ Same Alteration
- ☒ FDA Approved Drugs
- ☒ FDA Approved Targeted Cancer Drugs

Category 1: FDA-approved drugs for which alterations in these genes/proteins are approved biomarkers in this tumor type:
Show 10 entries Search:

Note

1 There are no recommended therapies in this category.

Showing 1 to 1 of 1 entries Previous 1 Next

Additional options to display only FDA-approved drugs or only FDA-approved targeted cancer drugs for categories 3 and 4 vs all drugs in DrugBank

4) Step-by-step analysis for built-in patient use case scenario

We now show the results for the different categories for the built-in example, of a potential patient with colorectal cancer and a G13V mutation in KRAS, a G1049S mutation PIK3CA, and a deleterious mutation in BRCA2. Note that there are no recommended Category 1 therapies for this patient:

Therapy recommendations using biological networks

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Colorectal cancer

Input tsv or csv file with molecular alterations
Browse... No file selected

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Gene_protein	Data_type	Alteration
KRAS	mutation	G13V
PIK3CA	mutation	G1049S
BRCA2	mutation	deleterious

Filter Recommended Therapies

- ☒ Same Cancer Type
- ☒ Same Alteration
- ☒ FDA Approved Drugs
- ☒ FDA Approved Targeted Cancer Drugs

Category 1: FDA-approved drugs for which alterations in these genes/proteins are approved biomarkers in this tumor type:
Show 10 entries Search:

Note

1 There are no recommended therapies in this category.

Showing 1 to 1 of 1 entries Previous 1 Next

We observe that there are a number of recommended Category 2 therapies, which are approved for deleterious BRCA2 mutations in breast, ovarian, fallopian tube, or primary peritoneal cancers. We note that g.mutation stands for “germline mutation:”

Therapy recommendations using biological networks

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Colorectal cancer

Input tsv or csv file with molecular alterations

Browse... No file selected

If a file is not uploaded, an example profile is loaded into the app.

Gene_protein	Data_type	Alteration
KRAS	mutation	G13V
PIK3CA	mutation	G1049S
BRCA2	mutation	deleterious

Filter Recommended Therapies

☐ Same Cancer Type
☒ Same Alteration
☒ FDA Approved Drugs
☒ FDA Approved Targeted Cancer Drugs

Category 2: FDA-approved drugs for which alterations in these genes/proteins are approved biomarkers in other tumor types:

Show 10 entries

Search:

	Drug	Gene or Protein	Type	Alteration	Tumor in which it is approved
1	OLAPARIB	BRCA2	g.mutation	deleterious	Breast cancer
2	OLAPARIB	BRCA2	g.mutation	deleterious	Ovarian cancer
3	RUCAPARIB	BRCA2	mutation	deleterious	Fallopian tube cancer
4	RUCAPARIB	BRCA2	mutation	deleterious	Ovarian cancer
5	RUCAPARIB	BRCA2	mutation	deleterious	Primary peritoneal cancer

Showing 1 to 5 of 5 entries

Previous 1 Next

Moving on to Category 3 therapies, we can now also see a visualization of our network-based approach using a Sankey diagram, which provides PubChem links for selected therapies, as well as the ability to mouse over the edges to obtain information on how they connect the nodes. Category 3 therapies have targets downstream of the input oncogenes, considering only the KEGG pathway corresponding to the input cancer type. In this scenario, the recommended therapies include BRAF and MEK inhibitors:

Therapy recommendations using biological networks

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Colorectal cancer

Input tsv or csv file with molecular alterations

Browse... No file selected

If a file is not uploaded, an example profile is loaded into the app.

Gene_protein	Data_type	Alteration
KRAS	mutation	G13V
PIK3CA	mutation	G1049S
BRCA2	mutation	deleterious

Filter Recommended Therapies

☒ Same Cancer Type
☐ Same Alteration
☒ FDA Approved Drugs
☒ FDA Approved Targeted Cancer Drugs

Preprint available on [Biorxiv](#)

Data sources

[DailyMed](#)
<https://pubchem.ncbi.nlm.nih.gov>

Category 3: FDA-approved drugs that either have as targets these alterations or genes/proteins or as biomarkers or targets other alterations or genes/proteins in the KEGG pathway corresponding to the specific cancer type, as well as additional drugs that have the above-mentioned genes/proteins as targets. Only consider the genes/proteins downstream of the genes/proteins found altered via molecular profiling that are also specified as oncogenes (in that cancer type) for the specific cancer type in KEGG.

Info panel

Therapy Selected: COBIMETINIB

PubChem link for selected therapies

[PubChem](#) > [COBIMETINIB](#) > [3D CONFORMER](#)
 CID 16222096
Cobimeti PubChem
3D Conformer
 Interactive Chemical Structure Model
☒ Ball and Stick ☐ Wire-Frame ☐ S
☒ Show Hydrogens ☐ Animate

We can also explore the results for Categories 3 and 4 in more detail via a sortable and searchable table:

	Drug	Gene or Protein	Type	Alteration	Path	Tumor in which it is approved	Predicted effect
1	COBIMETINIB	BRAF	mutation	V600E	KRAS -> BRAF	Melanoma	sensitive
2	COBIMETINIB	BRAF	mutation	V600K	KRAS -> BRAF	Melanoma	sensitive
3	DABRAFENIB	BRAF	mutation	V600E	KRAS -> BRAF	Non-small cell lung cancer	sensitive
4	DABRAFENIB	BRAF	mutation	V600E	KRAS -> BRAF	Melanoma	sensitive
5	DABRAFENIB	BRAF	mutation	V600K	KRAS -> BRAF	Melanoma	sensitive
6	DABRAFENIB	BRAF	mutation	V600E	KRAS -> BRAF	Anaplastic thyroid cancer	sensitive
12	TRAMETINIB	BRAF	mutation	V600E	KRAS -> BRAF	Non-small cell lung cancer	sensitive
13	TRAMETINIB	BRAF	mutation	V600E	KRAS -> BRAF	Melanoma	sensitive
14	TRAMETINIB	BRAF	mutation	V600K	KRAS -> BRAF	Melanoma	sensitive
15	TRAMETINIB	BRAF	mutation	V600E	KRAS -> BRAF	Anaplastic thyroid cancer	sensitive

Showing 1 to 10 of 45 entries

Previous 1 2 3 4 5 Next

If instead we look at all FDA-approved drugs, the number of therapies increases rapidly:

Therapy recommendations using biological networks

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Select cancer type

Colorectal cancer

Input tsv or csv file with molecular alterations

Browse... No file selected

If a file is not uploaded, an example profile is loaded into the app.

Gene_protein	Data_type	Alteration
KRAS	mutation	G13V
PIK3CA	mutation	G1049S
BRCA2	mutation	deleterious

Filter Recommended Therapies

☒ Same Cancer Type

☐ Same Alteration

☒ FDA Approved Drugs

☐ FDA Approved Targeted Cancer Drugs

Preprint available on [Biorxiv](#)

Data sources

- DailyMed
- KEGG

Category 3: FDA-approved drugs that either have as targets these alterations or genes/proteins or as biomarkers or targets other alterations or genes/proteins in the KEGG pathway corresponding to the specific cancer type, as well as additional drugs that have the above-mentioned genes/proteins as targets. Only consider the genes/proteins downstream of the genes/proteins found altered via molecular profiling that are also specified as oncogenes (in that cancer type) for the specific cancer type in KEGG.

Info panel

Therapy Selected: AZATHIOPRINE

[PUBCHEM](#) > [AZATHIOPRINE](#) > [3D CONFORMER](#)

CID 2265

Azathioprine

3D Conformer

Interactive Chemical Structure Model

☒ Ball and Stick ☐ Sticks

☐ Wire-Frame ☐ Space-Filling

☒ Show Hydrogens

☐ Animate

We can also expand further to all drugs in DrugBank:

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Finally, we can look at Category 4 therapies. These are based on targets downstream of the input oncogenes using all the KEGG cancer pathways, not just the pathway corresponding to the input cancer type:

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Select cancer type
Colorectal cancer

Input tsv or csv file with molecular alterations
Browse... No file selected

If a file is not uploaded, an example profile is loaded into the app.

Gene_protein	Data_type	Alteration
KRAS	mutation	G13V
PIK3CA	mutation	G1049S
BRCA2	mutation	deleterious

Filter Cancer Therapies

☒ Same Cancer Type
☐ Same Alteration
☐ FDA Approved Targeted Cancer Drugs

Preprint available on [Biorxiv](#)

Data sources
DailyMed

Molecular Profile
BRCA21
KRAS

Inferred Targets
ERBB2
EGFR
PDGFRB
NRAS
IMTOR
IMET
IGF1R
IVEGFA
IMAP2K2
CDK2
IAR
PDGFRA
CDK4
CDK6
IFGFR2
IFGFR1
JAK1

Recommended Therapies
ADO, TRASTUZUMAB, EMTANSII, ERTINIB, MESYCLORIDE, IMATINIB, MESYCLATE, LAPATINIB, DEPARINIB, BEVACIZUMAB, EVEROLIMUS, BRIGATINIB, BRA-CIZUMAB, BOS-TINIB, MONOHYDRATE, VANDETANIB, CAPECITABINE, PONIATINIB, HYDROCHLORIDE, BICICUTINIB, LEVATINIB, SORAFENIB, TRASTUZUMAB, REGORAFENIB, SUINIBIN, MALATE, APERCUTINIB, PARZOLINE, HYDROCHLORIDE, ERTINIB, ZIV-FLIBERCEPT

FDA Approved Drugs
OLAPARIB
RUCAPARIB

Info panel
Therapy Selected: AFATINIB
PUBCHEM > AFATINIB > 3D CONFORMER
CID: 10184653
Afatinib
3D Conformer
Interactive Chemical Structure Model
Ball and Stick
Sticks
Wire-Frame
Space-Filling
Show Hydrogens
Animate