The CDGnet tool consists of an evidence-based network approach for recommending targeted cancer therapies. It is currently hosted at <a href="http://epiviz.cbcb.umd.edu/shiny/CDGnet/">http://epiviz.cbcb.umd.edu/shiny/CDGnet/</a>, with the code being available at <a href="https://github.com/SiminaB/CDGnet/">https://epiviz.cbcb.umd.edu/shiny/CDGnet/</a>, with the code being available at <a href="https://github.com/SiminaB/CDGnet/">https://github.com/SiminaB/CDGnet/</a>. A preprint describing it within the scientific context is available at <a href="https://www.biorxiv.org/content/10.1101/605261v1">https://www.biorxiv.org/content/10.1101/605261v1</a>. Its goal is to **prioritize targeted therapy assigned**<a href="for cancer patients using drug-gene networks">for cancer patients using drug-gene networks</a>. These networks include information from biological pathways, specially by looking at <a href="targets downstream of oncogenes">targets downstream of oncogenes</a> (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.

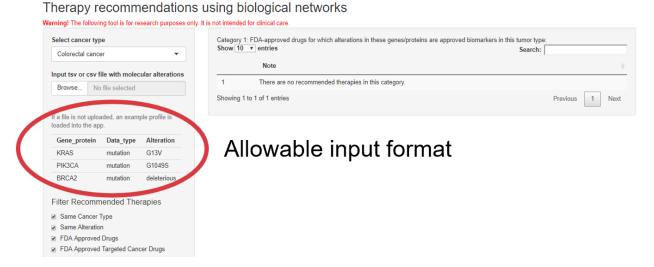
Please note that this tool is for research purposes only. It is not intended for clinical care.

## 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:

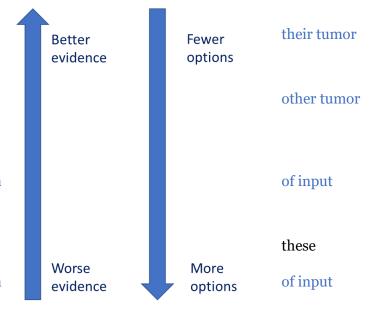


We also provide an example for a tumor that is ER+ and has overexpression of FGFR1 (both csv and tsv files) at <a href="https://github.com/SiminaB/CDGnet/tree/master/data">https://github.com/SiminaB/CDGnet/tree/master/data</a>; this example is also used in the preprint for a putative breast cancer patient. 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 type
- 2. FDA-approved drugs for which the patient's alterations/genes/proteins are biomarkers in types
- 3. Drugs which have as targets these alterations/genes/proteins or as biomarkers/targets others that are downstream oncogenes when considering the pathway corresponding to this tumor type.\*
- 4. Drugs which have as targets/biomarkers either alterations/genes/proteins or as biomarkers/targets others that are downstream oncogenes when considering the pathways corresponding to other tumor types.\*

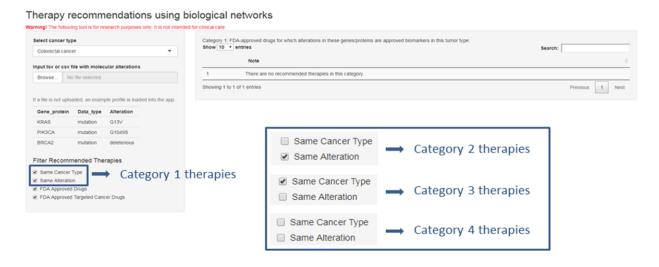


<sup>\*</sup> Could be targeted drugs prescribed for their tumor type or other tumor types OR any FDA-approved drug OR any drug in DrugBank.

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:



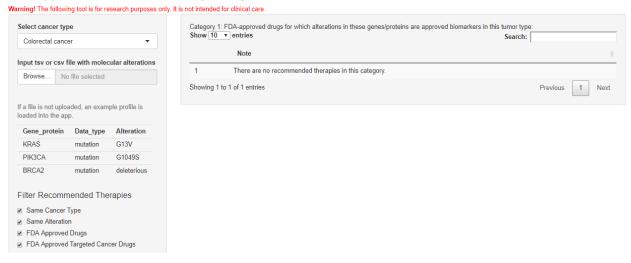
Additionally, for Categories 3 and 4, users may choose to display only FDA-approved drugs or only FDA-approved targeted cancer drugs vs. all drugs in DrugBank:

Therapy recommendations using biological networks Warning! The following tool is for research purposes only. It is not intended for clinical care Category 1: FDA-approved drugs for which alterations in these genes/proteins are approved biomarkers in this tumor type Show 10 v entries Search: Select cancer type Search: Colorectal cancer Input tsv or csv file with molecular alterations There are no recommended therapies in this category Browse... No file selected Showing 1 to 1 of 1 entries Previous 1 Next Gene\_protein Data\_type Alteration KRAS mutation G13V mutation G1049S PIK3CA Additional options to display only FDA-approved drugs or only FDA-approved targeted cancer Filter Recommended Therapies drugs for categories 3 and 4 vs all drugs in FDA Approved Drugs DrugBank FDA Approved Targeted Cancer Drugs

# 4) Step-by-step analysis for built-in example

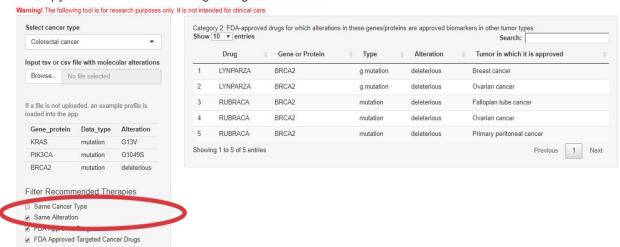
We now show the results for the different categories for the built-in example, of a patient with colorectal cancer and a G13V mutation in KRAS, a G1049S mutation PIK3CA, and a deleterious mutation in BRCA2. Note that there are no recommended Category 1 therapies for this patient:

Therapy recommendations using biological networks

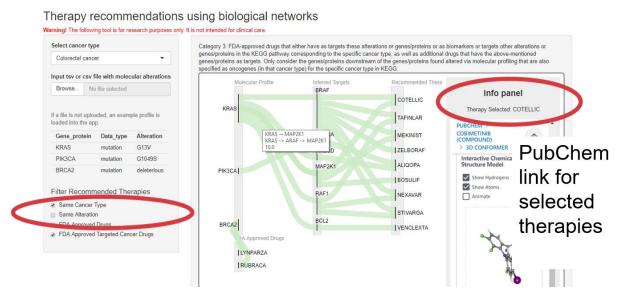


We observe that there are a number of recommended Category 2 therapies, which are approved for deleterious BRCA2 mutations in breast, ovarian, fallopian tube, or primary peritoneal cancers. We note that g.mutation stands for "germline mutation:"

#### Therapy recommendations using biological networks



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:

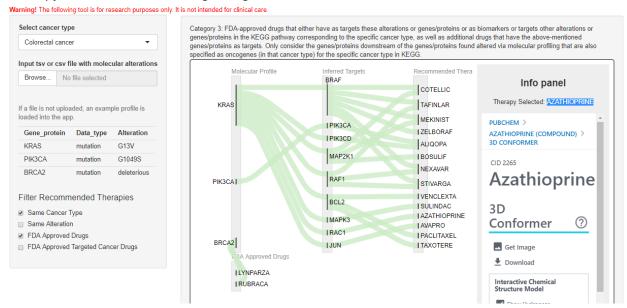


We can also explore the results for Categories 3 and 4 in more detail via a sortable and searchable table:

	Drug \$	Gene or Protein		Alteration \$	Path \$	Tumor in which it is approved	Predicted effect
1	COTELLIC	BRAF	mutation	V600E	KRAS -> BRAF	Melanoma	sensitive
2	COTELLIC	BRAF	mutation	V600K	KRAS -> BRAF	Melanoma	sensitive
3	TAFINLAR	BRAF	mutation	V600E	KRAS -> BRAF	Non-small cell lung cancer	sensitive
4	TAFINLAR	BRAF	mutation	V600E	KRAS -> BRAF	Melanoma	sensitive
5	TAFINLAR	BRAF	mutation	V600K	KRAS -> BRAF	Melanoma	sensitive
6	TAFINLAR	BRAF	mutation	V600E	KRAS -> BRAF	Anaplastic thyroid cancer	sensitive
12	MEKINIST	BRAF	mutation	V600E	KRAS -> BRAF	Non-small cell lung cancer	sensitive

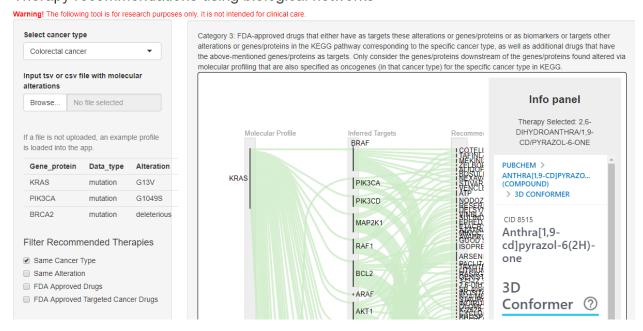
If instead we look at all FDA-approved drugs, the number of therapies increases rapidly:

Therapy recommendations using biological networks



We can also expand further to all drugs in DrugBank:

### Therapy recommendations using biological networks



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:

