

# Using Patient-Specific Drug-Gene Networks for Recommending Targeted Cancer Therapies

S33: Oral Presentations - Cancer and Genetics Informatics

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#IS19



I and my spouse/partner have no relevant relationships with commercial interests to disclose.

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# What is precision oncology?

Precision oncology refers to tailoring interventions to patients in ways that go beyond traditional characteristics of age, sex, disease, symptoms etc by considering **biomarkers**.

Biomarkers may be:

- **genetic characteristics**: can be either *germline* (inherited, in normal tissue) or *somatic* (in cancer cells but not normal tissue)
- **mRNA or protein expression values**: refer to expression in tumors, either in comparison to other tumors or to adjacent normal tissues

# Tumor molecular profiling (MP)

It is now routine to perform **molecular profiling** (MP) in certain tumor types to check for specific molecular features at diagnosis to decide on a **targeted treatment plan** eg:

- KRAS-wild type (non-mutated) colorectal cancer is treated with EGFR inhibitors (**DNA alteration**)
- ER+ breast cancer is treated with tamoxifen and fulvestrant, HER2+ breast cancer is treated with trastuzumab (**mRNA/protein expression**)

In many cases tumor MP is used after a patient has progressed on multiple lines of therapy and/or has few/no therapy options left.

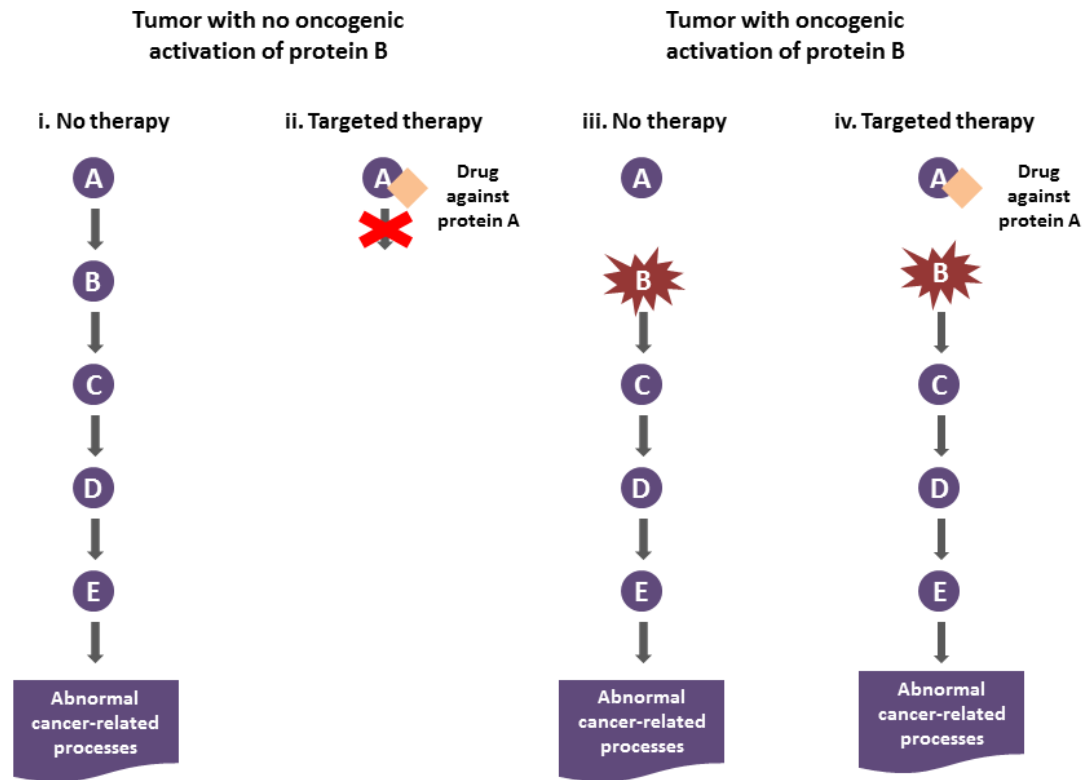
- Patient may then receive an off-label therapy that is prescribed for their alteration in another tumor type

# Want to enrich this by including biological pathway information

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How do we do this?

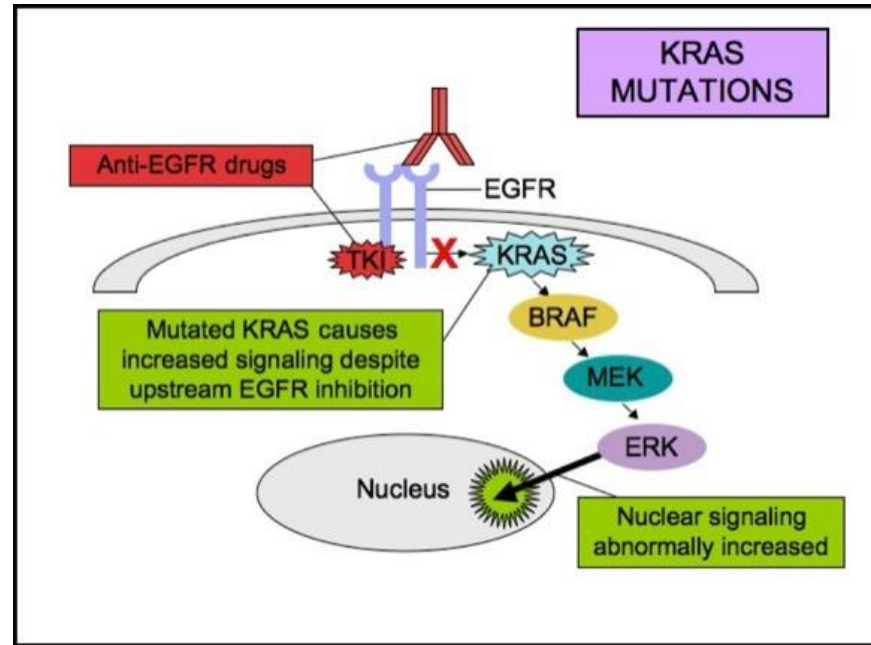
# Downstream targets of oncogenes



# EGFR inhibitors for KRAS-wild type colorectal tumors

Mutated KRAS means patients are not likely to respond to EGFR inhibitors

<https://www.cancercommons.org/wordpress/wp-content/uploads/2017/05/kRAS-mutations.jpg>:





# Prioritize therapies with drug-gene networks

## CDGnet (cancer-drug-gene networks) tool

We prioritize therapies by creating networks by integrating (inputs in orange):

- Specific alterations found in a patient's tumor (eg G13V in KRAS, G1039S in PIK3CA mutations)
- Patient's cancer type (eg Colorectal cancer)
- Biological pathways relevant to cancer type, alterations (eg KEGG)
- FDA-approved targeted cancer therapies and indications (biomarker, cancer type)
- Drug-gene connections (drug targets) (eg DrugBank)
- Knowledge about activity of alterations/altered gene (eg gene is an oncogene)

# Current landing page

## 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

<http://epiviz.cbcb.umd.edu/shiny/CDGnet/>

# Current landing page

## Therapy recommendations using biological networks

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

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Input tsv or csv file with molecular alterations  
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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

Allowable input format

<http://epiviz.cbcb.umd.edu/shiny/CDGnet/>

# 4 ordered categories of therapies

1. FDA-approved drugs for which these alterations/genes/proteins are biomarkers **in this tumor type**
2. FDA-approved drugs for which these 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.

# Current landing page

## 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 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.

Category 1: Same cancer type + Same alteration

Category 2: NOT(Same cancer type) + Same alteration

Category 3: Same cancer type + NOT(Same alteration)

Category 4: NOT(Same cancer type) + NOT(Same alteration)

<http://epiviz.cbcb.umd.edu/shiny/CDGnet/>

# Current landing page

## 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

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

<http://epiviz.cbcb.umd.edu/shiny/CDGnet/>

# Category 1: No recommended therapies

## 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

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

<http://epiviz.cbcb.umd.edu/shiny/CDGnet/>

# Category 2: Therapies approved for BRCA2 mutations in breast, ovarian cancers

## 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 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	LYNPARZA	BRCA2	g.mutation	deleterious	Breast cancer
2	LYNPARZA	BRCA2	g.mutation	deleterious	Ovarian cancer
3	RUBRACA	BRCA2	mutation	deleterious	Fallopian tube cancer
4	RUBRACA	BRCA2	mutation	deleterious	Ovarian cancer
5	RUBRACA	BRCA2	mutation	deleterious	Primary peritoneal cancer

Showing 1 to 5 of 5 entries

Previous 1 Next

<http://epiviz.cbcb.umd.edu/shiny/CDGnet/>



# Category 3: Therapies include BRAF, 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

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.

Molecular Profile

Inferred Targets

Recommended Therapies

Info panel

Therapy Selected: COTELLIC

PUBCHEM  
COBIMETINIB  
(COMPOUND)  
> 3D CONFORMER

Interactive Chemical Structure Model

- ☒ Show Hydrogens
- ☒ Show Atoms
- ☐ Animate

PubChem link for selected therapies

<http://epiviz.cbcb.umd.edu/shiny/CDGnet/>

# Category 4: Therapies include MTOR, ERBB2, EGFR inhibitors

## 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

Category 4: 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 pathways corresponding to other cancer types, 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 for various cancer types in KEGG.

The diagram illustrates a biological network for Category 4. It is divided into three main sections: Molecular Profile, Inferred Targets, and Recommended Therapies. The Molecular Profile section lists KRAS and BRCA21. The Inferred Targets section lists ERBB2, EGFR, PDGFRB, and a group of targets including NRAS, MTOR, MET, IGF1R, VEGFA, MAP2K2, CDK2, IAR, PDGFRA, CDK4, CDK6, FGFR2, FGFR1, and JAK1. The Recommended Therapies section lists a large number of drugs including KADCYLA, GILTRIF, PARCEVA, GLEEVEC, TYKERB, NERLYNX, VEGFISOD, VEGFIBIA, PERLETA, AFNITOR, ALUNBRIG, AVASTIN, CARBOMETYX, CAPRELISA, ERLADA, ETRANCE, ICLUSIG, KADCYLA, KISQALVO, LERIVIN, MERINIST, NOLVADEX, PORTBAZZA, SPRYCEL, STIVARGA, SUTENT, TISULE, VERZENIO, VOTRIENT, ZANDRI, and ZALTRAP. Green lines connect the molecular profile to the inferred targets, and then to the recommended therapies.

Info panel

Therapy Selected: GILTRIF

PUBCHEM >  
AFATINIB DIMALEATE (COMPOUND)  
> 3D CONFORMER

CID 15606394  
Afatinib dimaleate

3D Conformer ?

Get Image  
Download

Interactive Chemical Structure Model of Parent  
CID 10184653

<http://epiviz.cbcb.umd.edu/shiny/CDGnet/>

# Current state and future development goals

- Shiny-based web application available at <http://epiviz.cbcb.umd.edu/shiny/CDGnet/>
- Code available at <https://github.com/SiminaB/CDGnet> and <https://github.com/jkanche/nfpmShinyComponent> (package for interactive visualization)
- Goals include:
  - Improved standardization, linkage between databases
  - Options to include other oncogenes, pathways (can currently do this by manually using code from Github repositories)
  - Connection to other resources (CIViC, clinical trials)
  - Expand networks to include resistance, feedback loops etc

# Thank you!

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