Visualizing patient-specific drug-gene networks for recommending targeted cancer therapies

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What is precision oncology?

Precision oncology (PO) 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

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

Prioritize targeted therapies using drug-gene networks

How do we expand the number of targeted therapy options available for consideration?

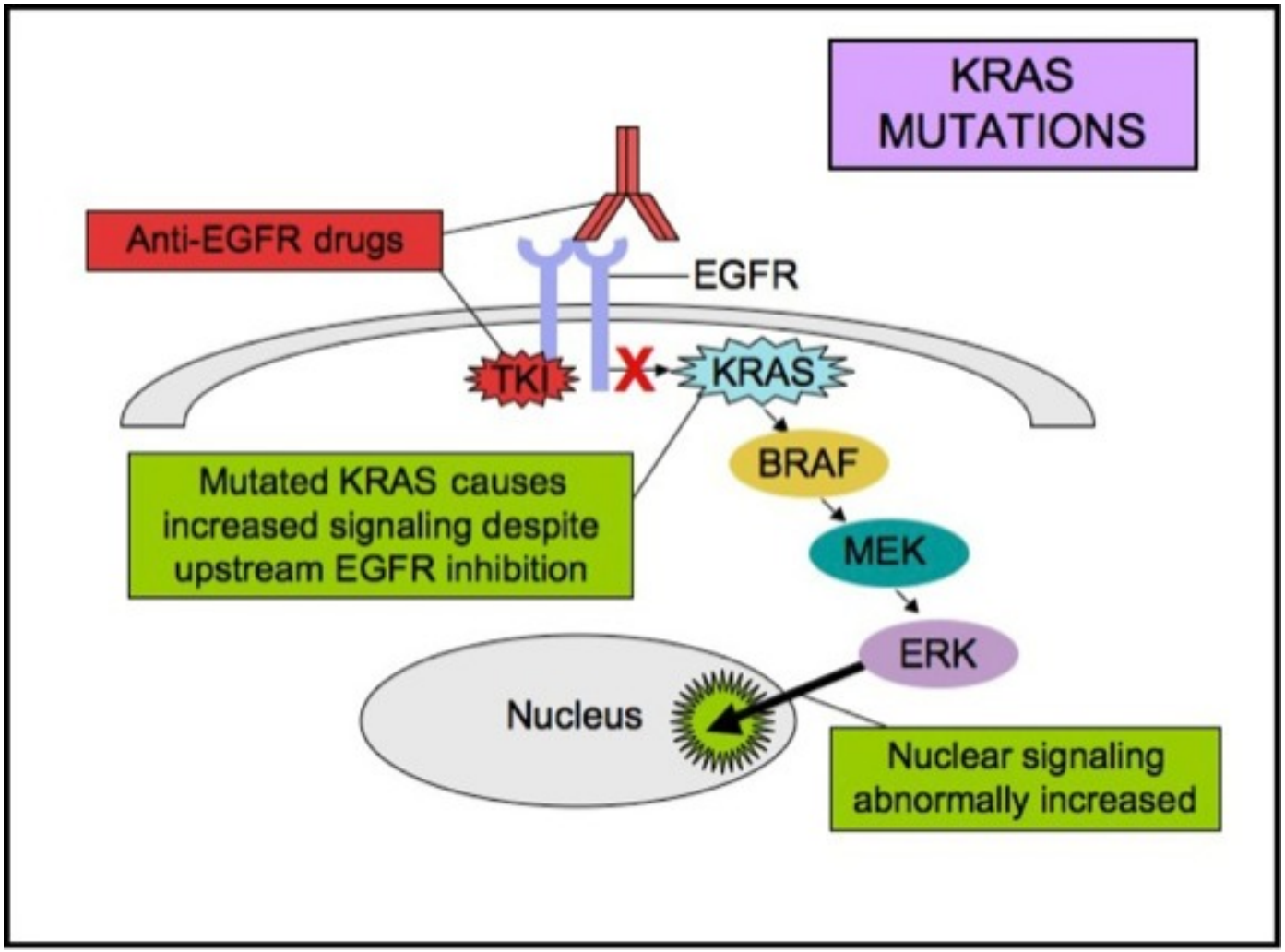
We can incorporate biological pathway information! Look at downstream targets of oncogenes.

Goal is to have an approach that is:

- automated
- personalized to individual patients
- as evidence-based as possible

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`:

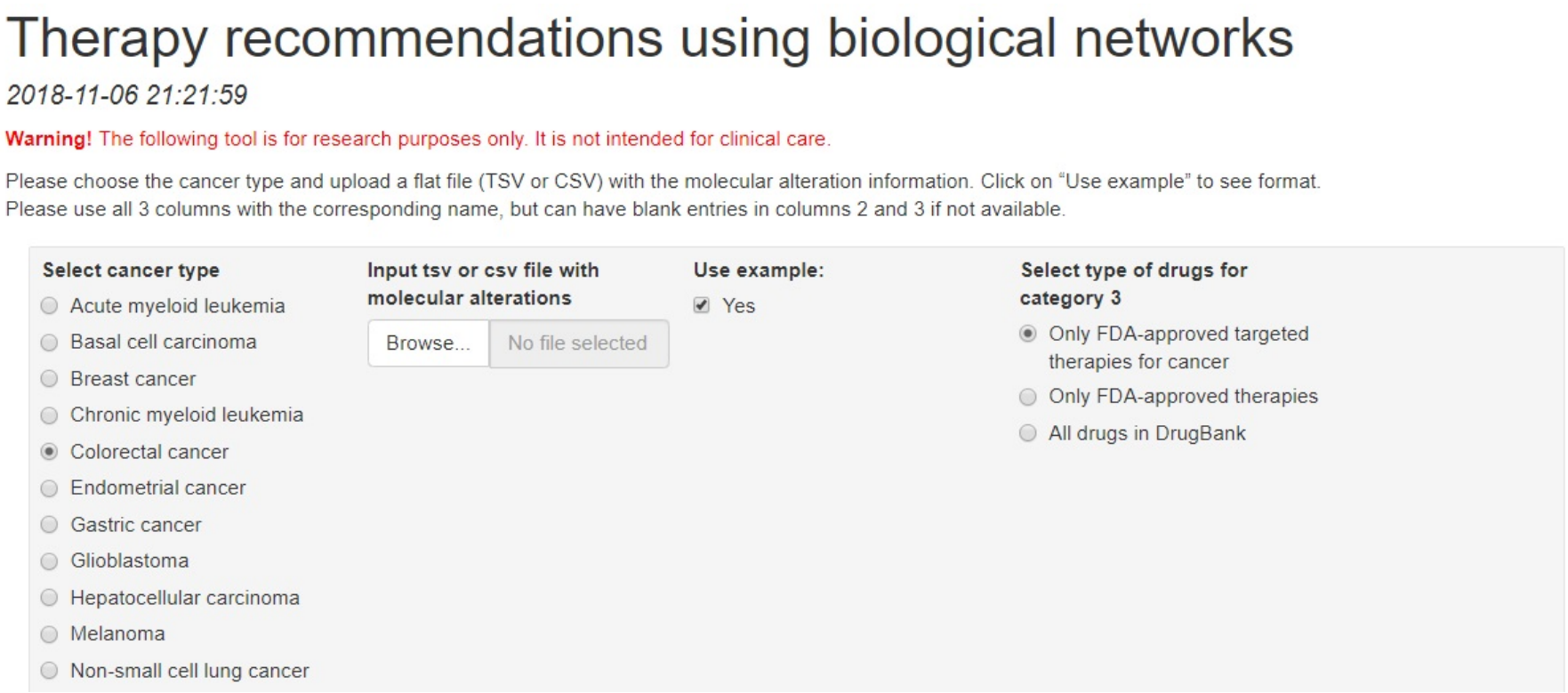


Prioritize targeted therapies using drug-gene networks

We prioritize targeted therapies by creating networks that integrate the following (inputs in orange):

- Specific alterations found in a patient's tumor
  - eg G13V in KRAS, pathogenic PIK3CA mutation
- 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



https://siminaboca.shinyapps.io/Search_MP_results_using_FDA_approvals_targets_KEGG/

Allowable input format

Alterations from molecular profiling (loaded by user):

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

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 for which these alterations/genes/proteins or others in the pathway corresponding to this tumor type are targets/biomarkers*
4. Drugs for which these alterations/genes/proteins or others in general cancer pathways are targets/biomarkers*

* They could be drugs prescribed for other tumor types

When considering pathways, currently looking just at portions of pathways downstream of oncogenes.

Example of current ordered recommendations

For the colorectal cancer patient with: G13V in KRAS, G1049S in PIK3CA mutation, deleterious mutation in BRCA2, the prioritization is:

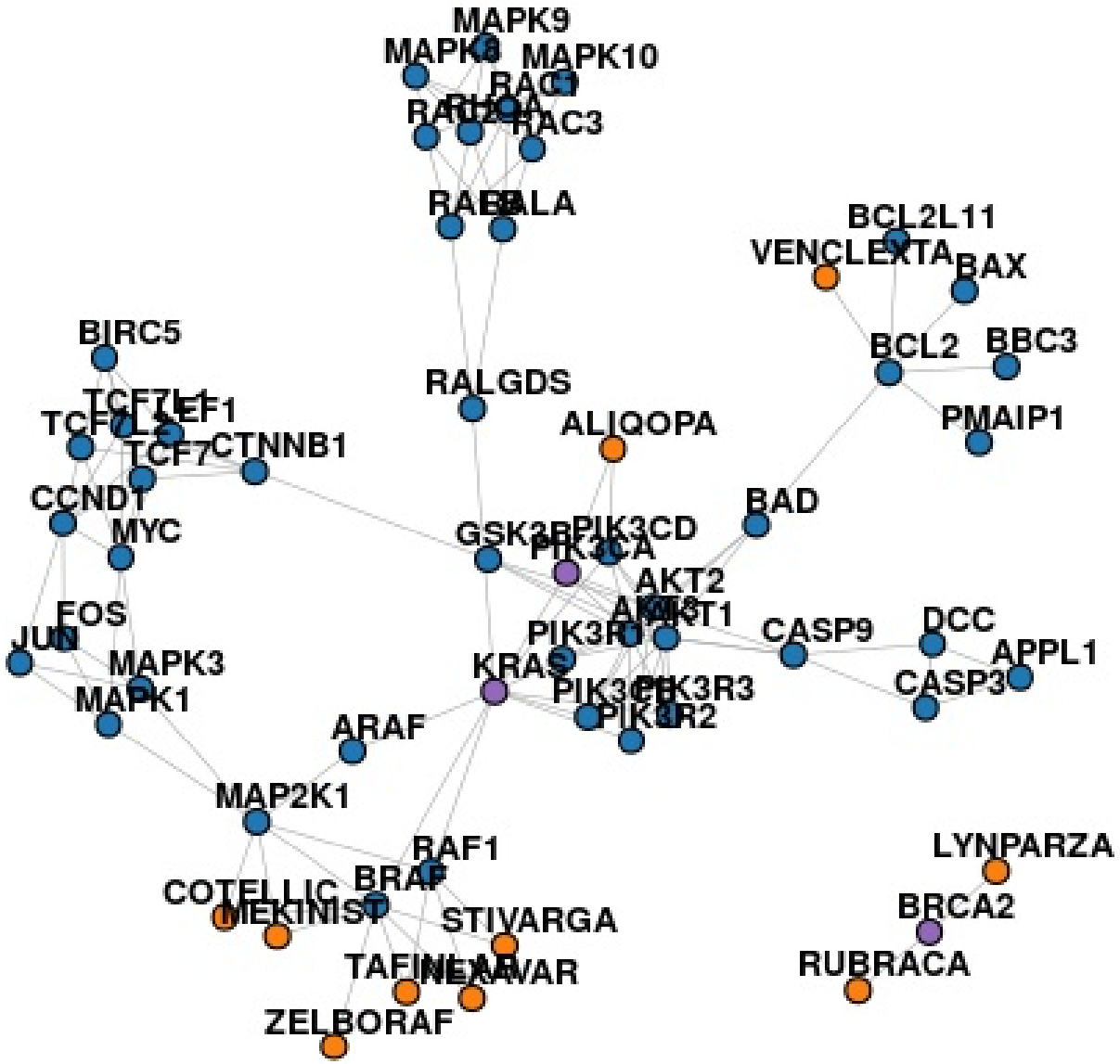
1. No recommended therapy
2. Olaparib and rucaparib
   - Approved in breast, ovarian, fallopian tube, or peritoneal cancers for BRCA2 mutations
3. BRAF inhibitors, MEK inhibitors*
   - Approved for melanoma non-small cell lung cancer with specific BRAF mutations
   - BRAF is downstream of KRAS in colorectal cancer
   - BRAF mutations are also biomarkers for MEK inhibitors
4. MTOR inhibitors, ERBB2 inhibitors, EGFR inhibitors*
   - Approved for a variety of tumors types
   - MTOR is downstream of KRAS and PIK3CA

* These are among the list of recommended therapies

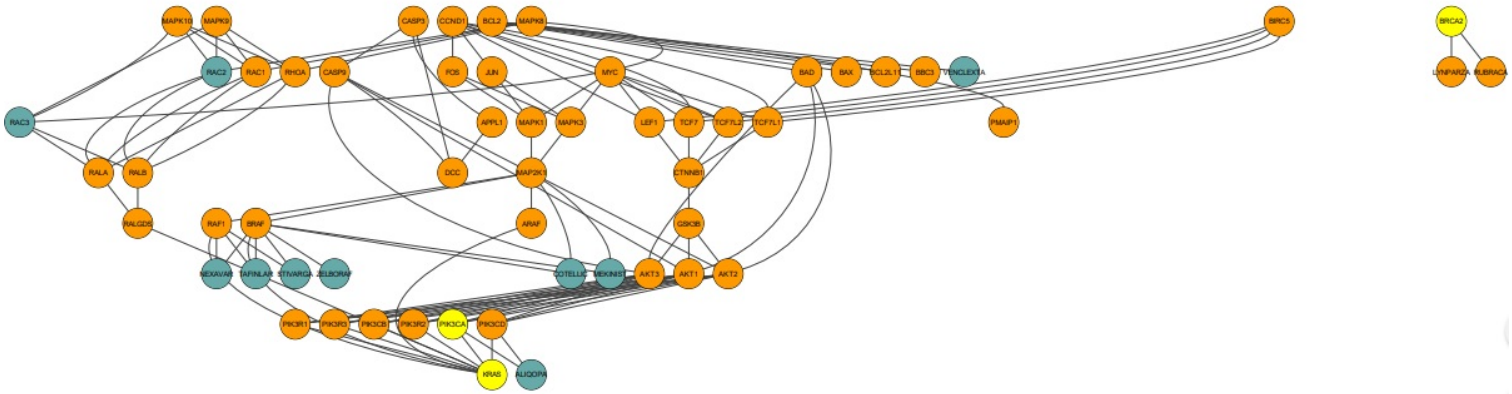
Example of category 3 recommendations

Drug	Gene or Protein	Type	Alteration	Path	Tumor in which it is approved	Predicted effect
COTELLIC	BRAF	mutation	V600E	KRAS -> BRAF	Melanoma	sensitive
COTELLIC	BRAF	mutation	V600K	KRAS -> BRAF	Melanoma	sensitive
TAFINLAR	BRAF	mutation	V600E	KRAS -> BRAF	Non-small cell lung cancer	sensitive
TAFINLAR	BRAF	mutation	V600E	KRAS -> BRAF	Melanoma	sensitive
TAFINLAR	BRAF	mutation	V600K	KRAS -> BRAF	Melanoma	sensitive
TAFINLAR	BRAF	mutation	V600E	KRAS -> BRAF	Anaplastic thyroid cancer	sensitive
MEKINIST	BRAF	mutation	V600E	KRAS -> BRAF	Non-small cell lung cancer	sensitive
MEKINIST	BRAF	mutation	V600E	KRAS -> BRAF	Melanoma	sensitive
MEKINIST	BRAF	mutation	V600K	KRAS -> BRAF	Melanoma	sensitive
MEKINIST	BRAF	mutation	V600E	KRAS -> BRAF	Anaplastic thyroid cancer	sensitive
ZELBORAF	BRAF	mutation	V600X	KRAS -> BRAF	Erdheim-Chester disease	sensitive
ZELBORAF	BRAF	mutation	V600E	KRAS -> BRAF	Melanoma	sensitive
ALIQOPA	PIK3CD	NA	NA	KRAS -> PIK3CD	Follicular lymphoma	target
ALIQOPA	PIK3CA	NA	NA	PIK3CA	Follicular lymphoma	target
COTELLIC	MAP2K1	NA	NA	KRAS -> ARAF -> MAP2K1	Melanoma	target
MEKINIST	MAP2K1	NA	NA	KRAS -> ARAF -> MAP2K1	Non-small cell lung cancer	target
MEKINIST	MAP2K1	NA	NA	KRAS -> ARAF -> MAP2K1	Melanoma	target
MEKINIST	MAP2K1	NA	NA	KRAS -> ARAF -> MAP2K1	Anaplastic thyroid cancer	target
NEXAVAR	RAF1	NA	NA	KRAS -> RAF1	Renal cell carcinoma	target
NEXAVAR	BRAF	NA	NA	KRAS -> BRAF	Renal cell carcinoma	target
NEXAVAR	RAF1	NA	NA	KRAS -> RAF1	Hepatocellular carcinoma	target
NEXAVAR	BRAF	NA	NA	KRAS -> BRAF	Hepatocellular carcinoma	target

Standard visualization

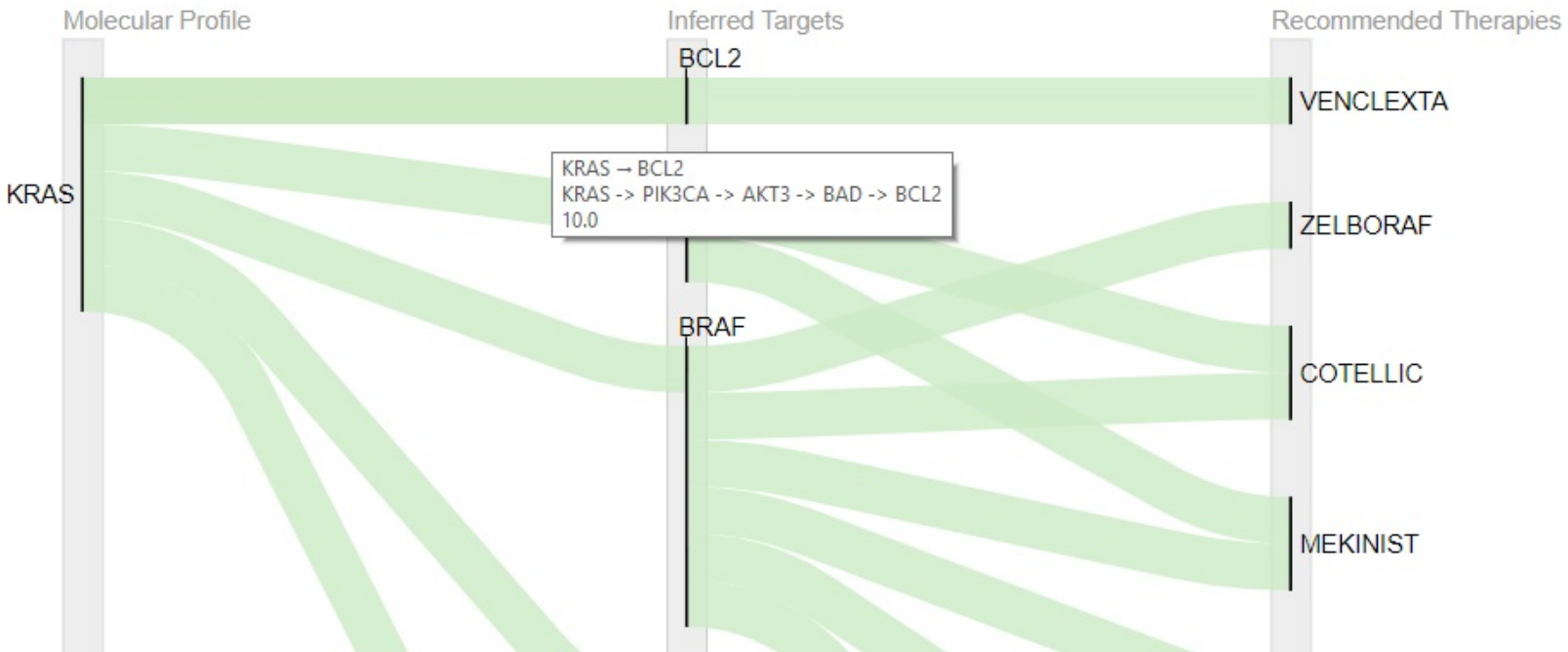


Standard Cytoscape visualization (connection with Cytoscape under development)



Visualization focusing on flow of evidence between drug-gene and gene-gene connections

Users can identify evidence that leads to a recommendation in an intuitive manner and connect to PubChem for more information on specific drugs.



Current development goals

- Order therapy recommendations by alteration they target
- Incorporate information on approved drug combinations and drug classes
- Connect to drug labels
- Expand number of pathways used
  - Currently just KEGG disease pathways
- Standardize mutation types, drug names, disease names using HGVS, MeSH terms etc.

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Questions?

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What is precision oncology?

Biomarkers essentially represent tests that are used to stratify individuals into 2 or more groups.

- Predictive biomarkers can be used to stratify patients into treatment groups with differential outcomes.
  e.g. “Patients with mutation X should be given treatment A instead of treatment B”
- Prognostic biomarkers are associated with different clinical outcomes for untreated or standard of care patients.
  e.g. “Patients with mutation X have better overall survival than patients without mutation X.”

Often use the term “molecular profiling” to refer to some test that considers one or more biomarkers.

How should a doctor assign a targeted therapy?

MP reports:

- Are used to inform choice of therapy for many cancer patients
- Present a list of therapies predicted to lead to benefit or lack of benefit
- Do not usually account for cross-talk within and between dysregulated pathways

Parenthetical remark on evidence-based aspect

- Precision medicine exemplifies the usual conflict between systematic, evidence-based analyses and timely and available information and care
- This tension can be seen in the lack of interaction between the systematic review (SR) and biocuration communities
  - SRs focus on systematic analysis of literature, pay great attention to risk of bias
  - Biocuration can be much faster than SRs and presents results in more easily digestible forms

Boca SM et al. “The future of evidence synthesis in precision oncology: Between systematic reviews and biocuration.” *JCO PO*, in press. `http://ascopubs.org/doi/full/10.1200/PO.17.00175`

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