

Developing software to build networks and perform data integration in precision oncology

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Acknowledgments

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Project goal

- Build a tool – **CDGnet** (Cancer Drug Gene networks) – to help researchers and eventually clinicians expand the number of targeted therapies available for individuals with cancer who have specific mutations (DNA changes) or genes/proteins that are overexpressed.

Precision oncology framework

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 and targeted therapies

It is now routine to perform **molecular profiling** 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 or fulvestrant, HER2+ breast cancer is treated with trastuzumab (**mRNA/protein expression**)

In many cases tumor molecular profiling 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
- Our goal with CDGnet is to **expand the number of possible targeted therapies and prioritize them using drug-gene network approaches**

CDGnet landing page and example user inputs

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

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

Previous1Next

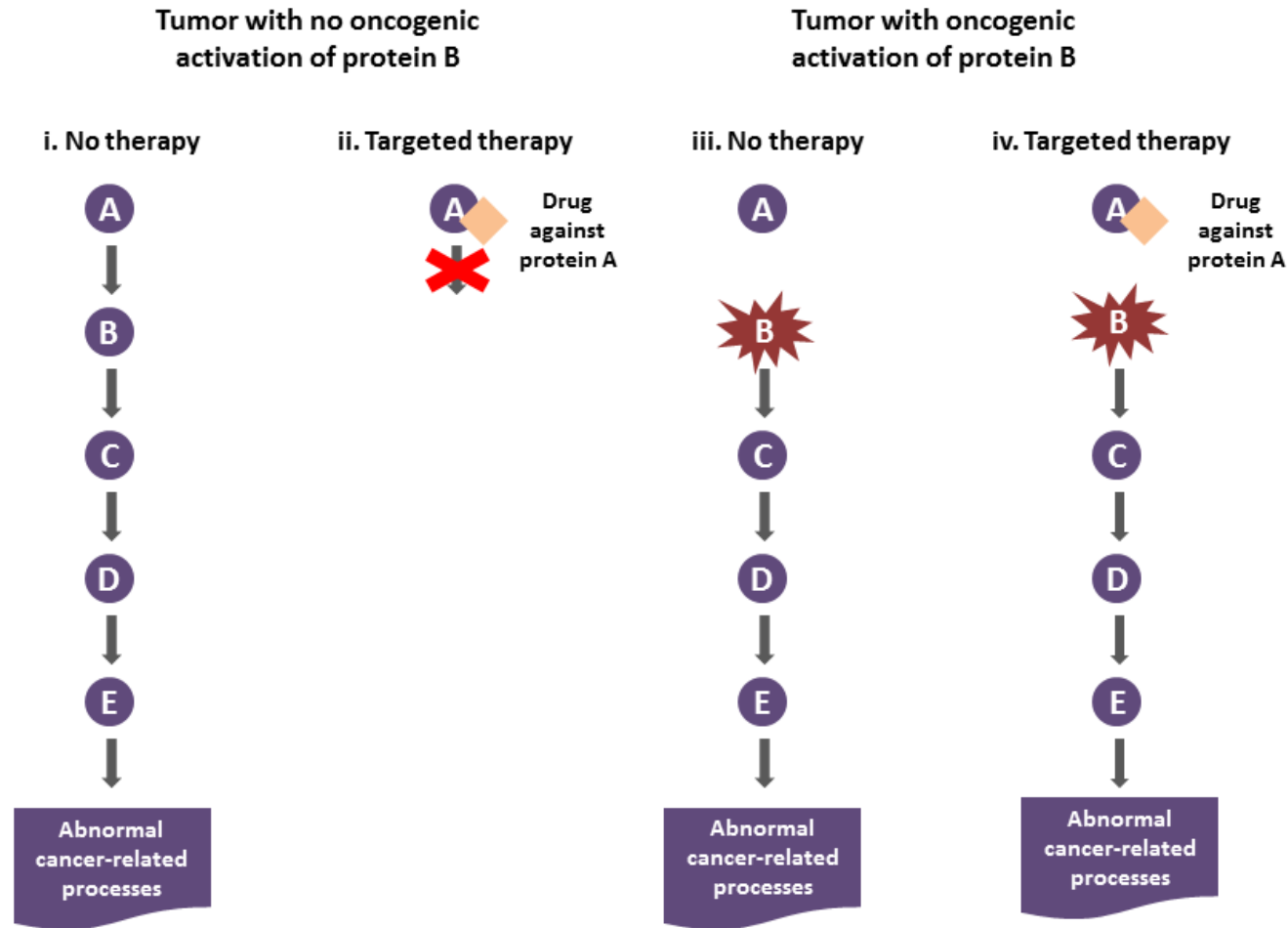
6

Want to enrich this by including biological pathway information

How do we do this?

How do we include pathway information?

Look at downstream targets of oncogenes



Therapy prioritization: 4 categories

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.

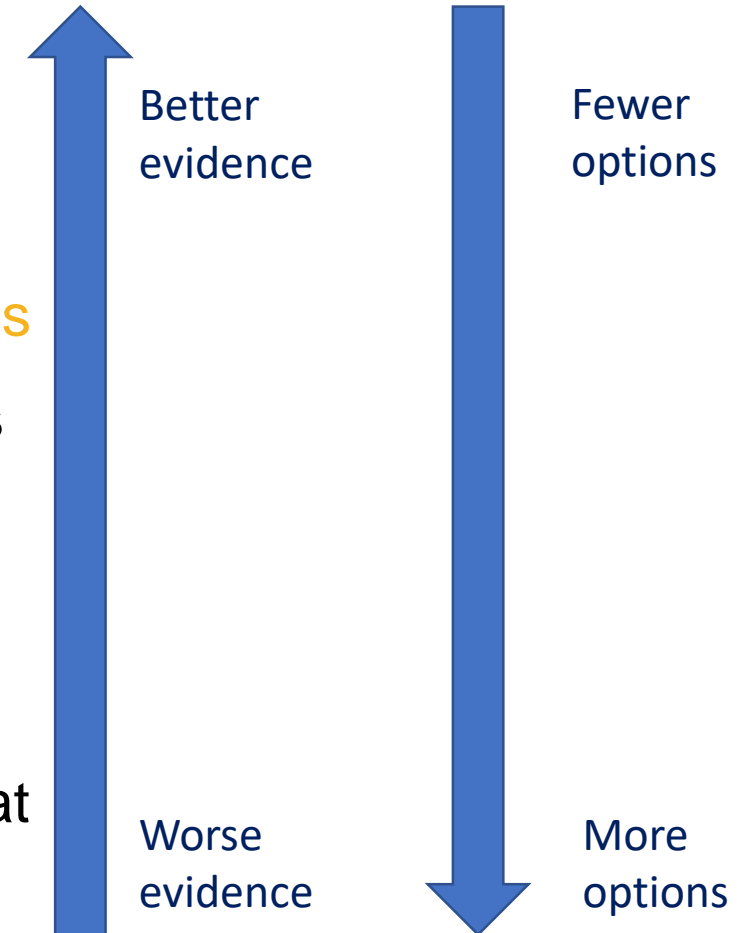
Our tool development goals

Have an approach that is:

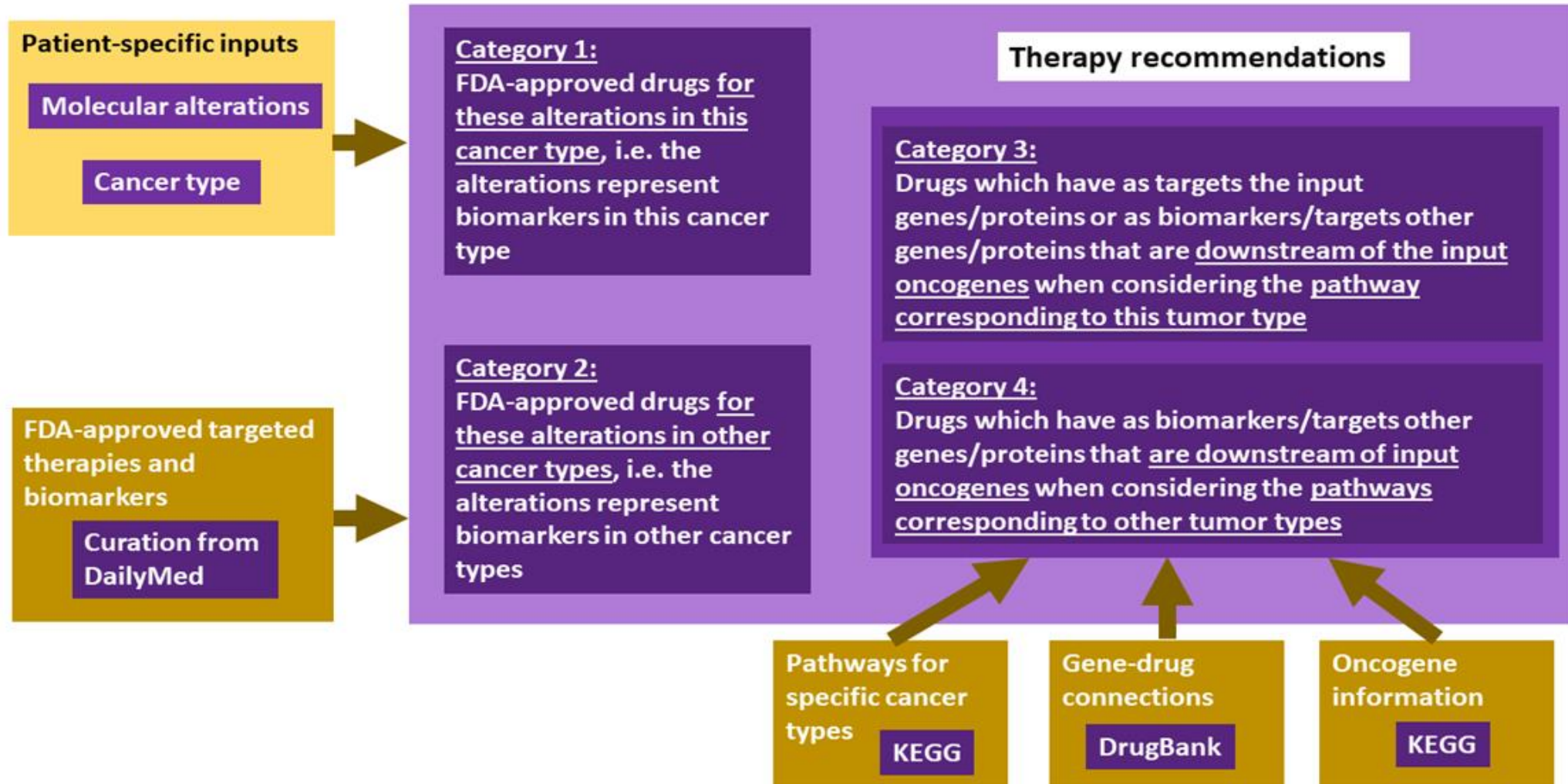
1. Automated
2. Transparent
3. Personalized to individual patients
4. Evidence-based

Therapy prioritization: 4 categories

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**.



General approach and data sources



Some important points

- This is currently a **data integration**, not a statistical project
- Results can be seen as **predictions for a single patient** or a population of patients with the same molecular profile and cancer type
- We looked for resources that are easy to use and integrate along with being transparent and evidence-based

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Filter Recommended Therapies

☒ Same Cancer Type → Category 1 therapies

☒ 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

☐ Same Cancer Type → Category 2 therapies

☒ Same Alteration

☒ Same Cancer Type → Category 3 therapies

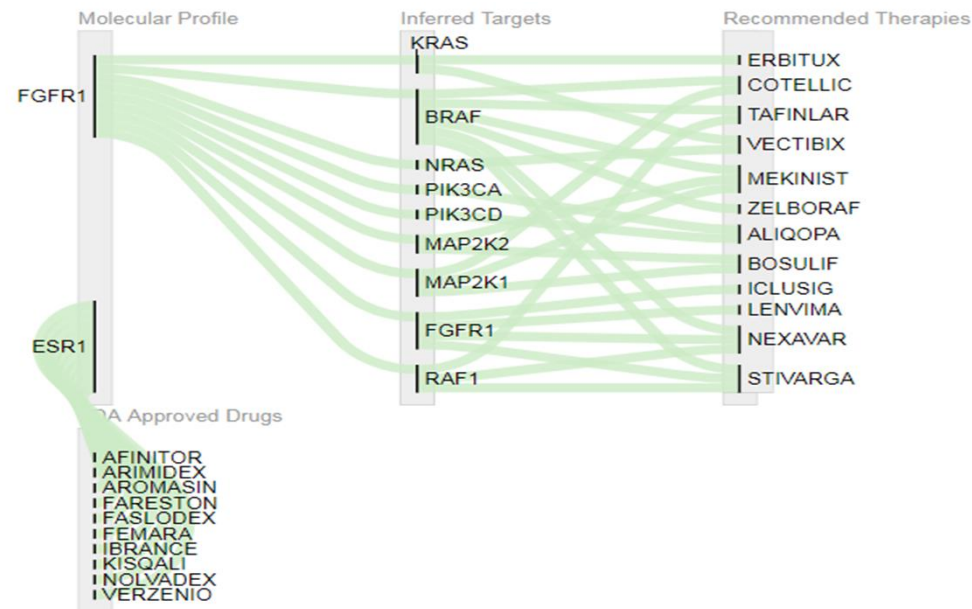
☐ Same Alteration

☐ Same Cancer Type → Category 4 therapies

☐ Same Alteration

CDGnet flow diagram example for category 3 recommendations

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



Info panel

Therapy Selected: TAFINLAR

PUBCHEM > DABRAFENIB (COMPOUND) > 3D CONFORMER

CID 44462760

Dabrafenib

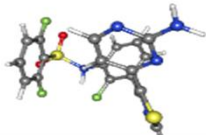
3D Conformer ?

Get Image

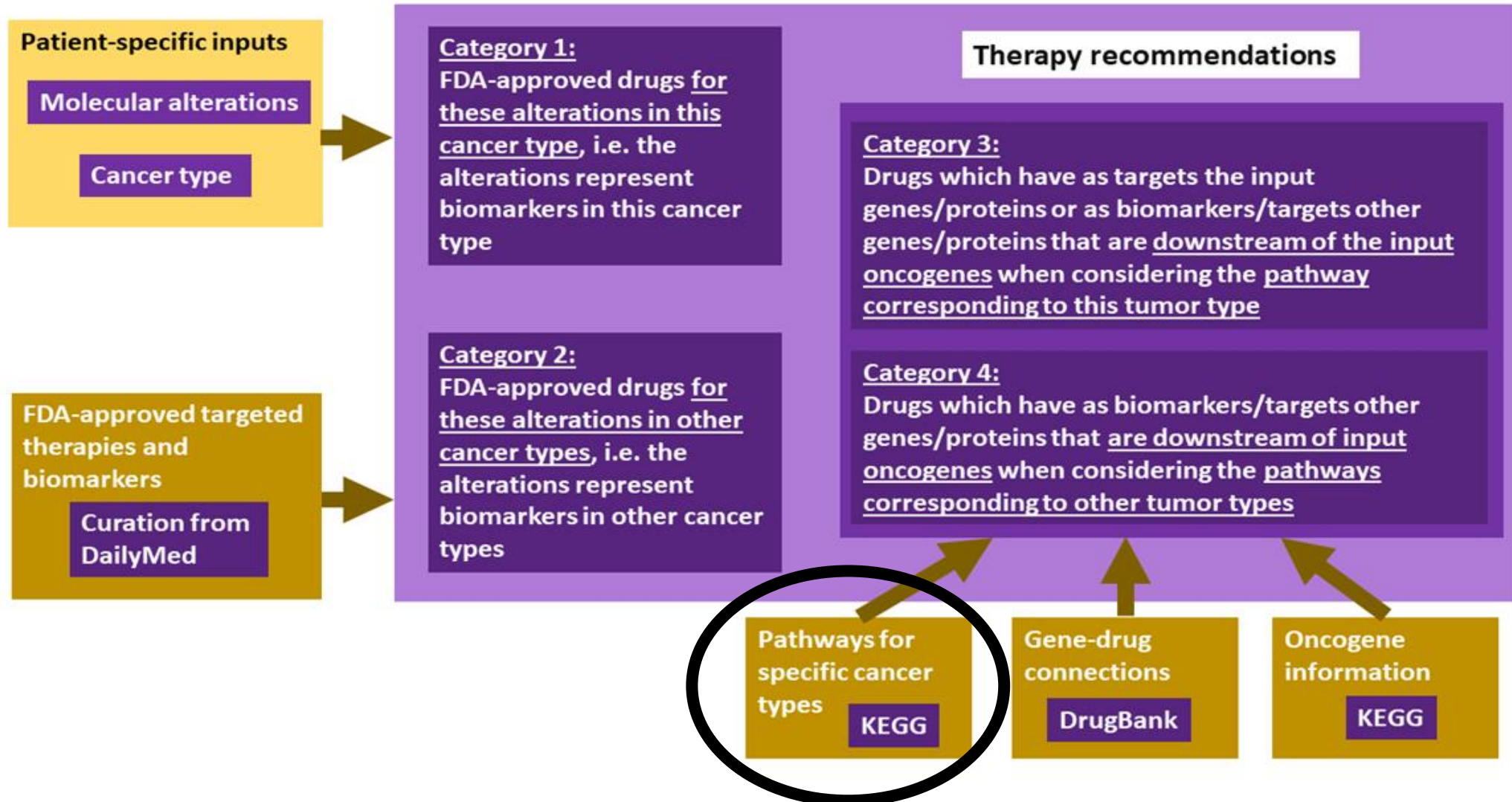
Download

Interactive Chemical Structure Model

- ☒ Show Hydrogens
- ☒ Show Atoms
- ☐ Animate



General approach and data sources



How did we choose the pathways?

- We are currently using the KEGG pathways
- **Benefits:**
 - Well-known, include pathways for many individual cancers
 - Expert-curated pathways
- **Issues:**
 - May not always agree with papers chosen by curators, some pathways are somewhat out of date
 - Not all cancer types included

KEGG.db

Bioconductor annotation data package

Description

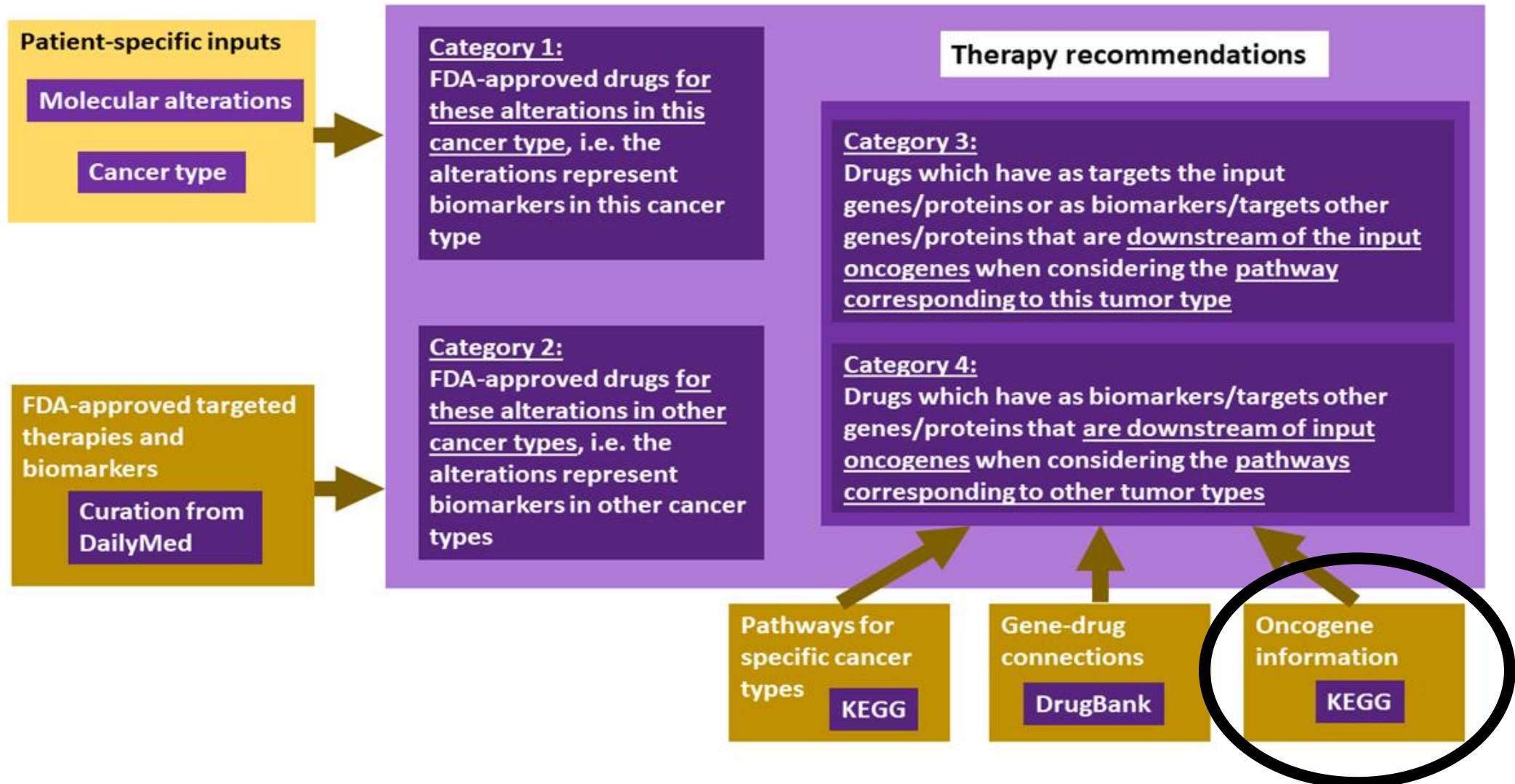
Welcome to the KEGG.db annotation Package. The purpose of this package was to provide detailed information about the latest version of the KEGG pathway databases. But a number of years ago, KEGG changed their policy about sharing their data and so this package is no longer allowed to be current. Users who are interested in a more current pathway data are encouraged to look at the KEGGREST or reactome.db packages.

Objects in this package are accessed using the `select()` interface. See `?select` in the AnnotationDbi package for details.

How did we choose the pathways?

- We are currently using the KEGG pathways
- **Benefits:**
 - Well-known, include pathways for many individual cancers
 - Expert-curated pathways
- **Issues:**
 - May not always agree with papers chosen by curators, some pathways are somewhat out of date
 - Not all cancer types included
 - Due to KEGG's policy, have the following approach to pulling in their data:
 - Use KEGGREST package to get access to KEGGREST API
 - Download all human pathways as KGML files (KEGG-specific XML files)
 - Use KEGGgraph package to convert KGML files into data frames
 - Use org.Hs.eg.db package to convert KEGG gene IDs to gene names
 - This approach makes it difficult to perform updates and harder for others to reproduce our work

General approach and data sources



How did we choose the oncogenes?

- We are currently using the oncogenes provided by KEGG for each cancer type
 - This ensures that we are considering the same cancer types for pathways and oncogenes
- Note that the same gene may not always be expressed or have the same function in all tissues so oncogenic activity often differs by tumor type
- Being classified as an “oncogene” is based on applying a threshold to results from a mathematical or statistical model
- For internal use, we are also considering the candidate oncogenes from the pan-TCGA paper:

Cell

Volume 173, Issue 2, 5 April 2018, Pages 371-385.e18

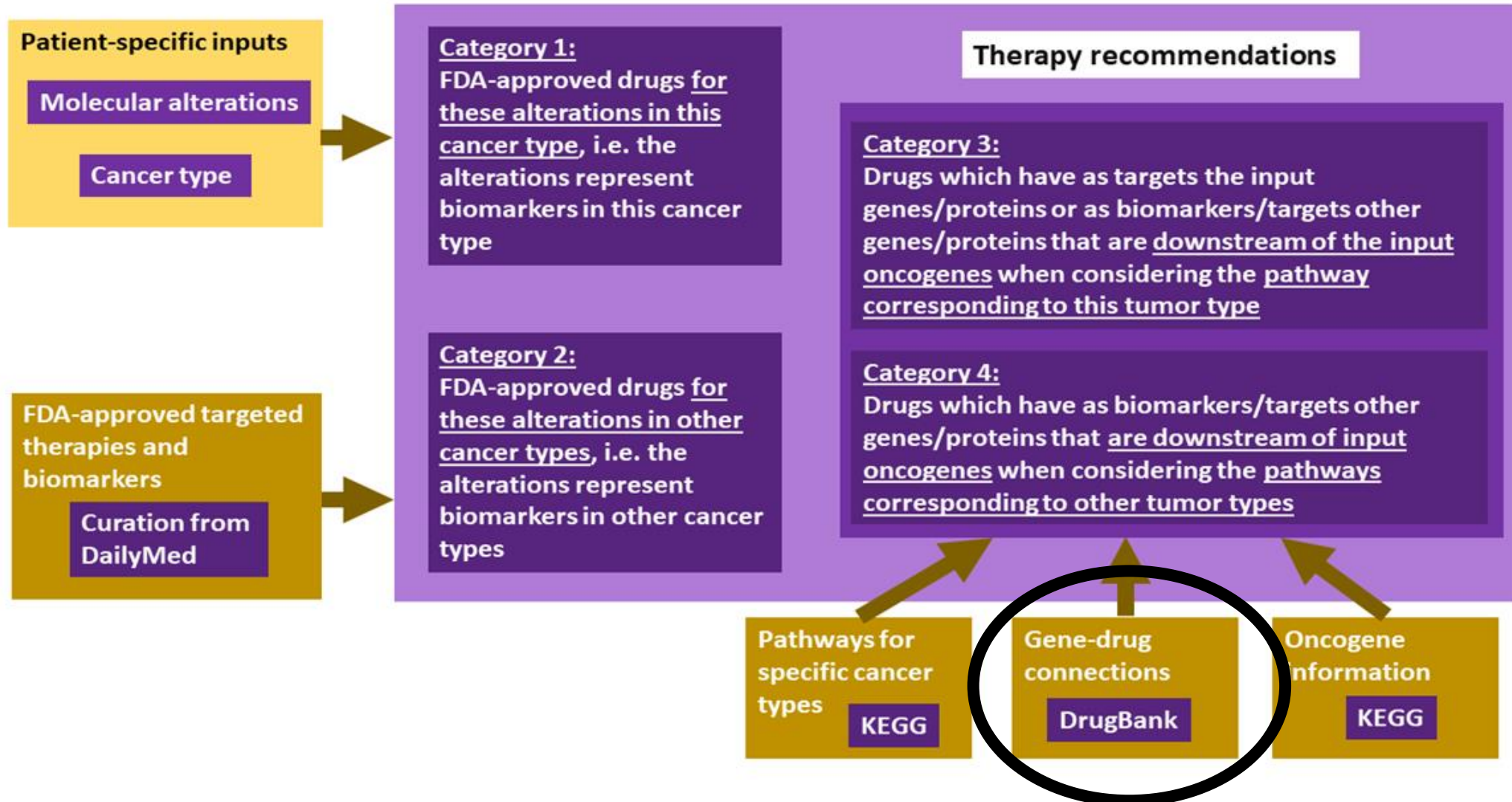
CellPress

Article

Comprehensive Characterization of Cancer Driver Genes and Mutations

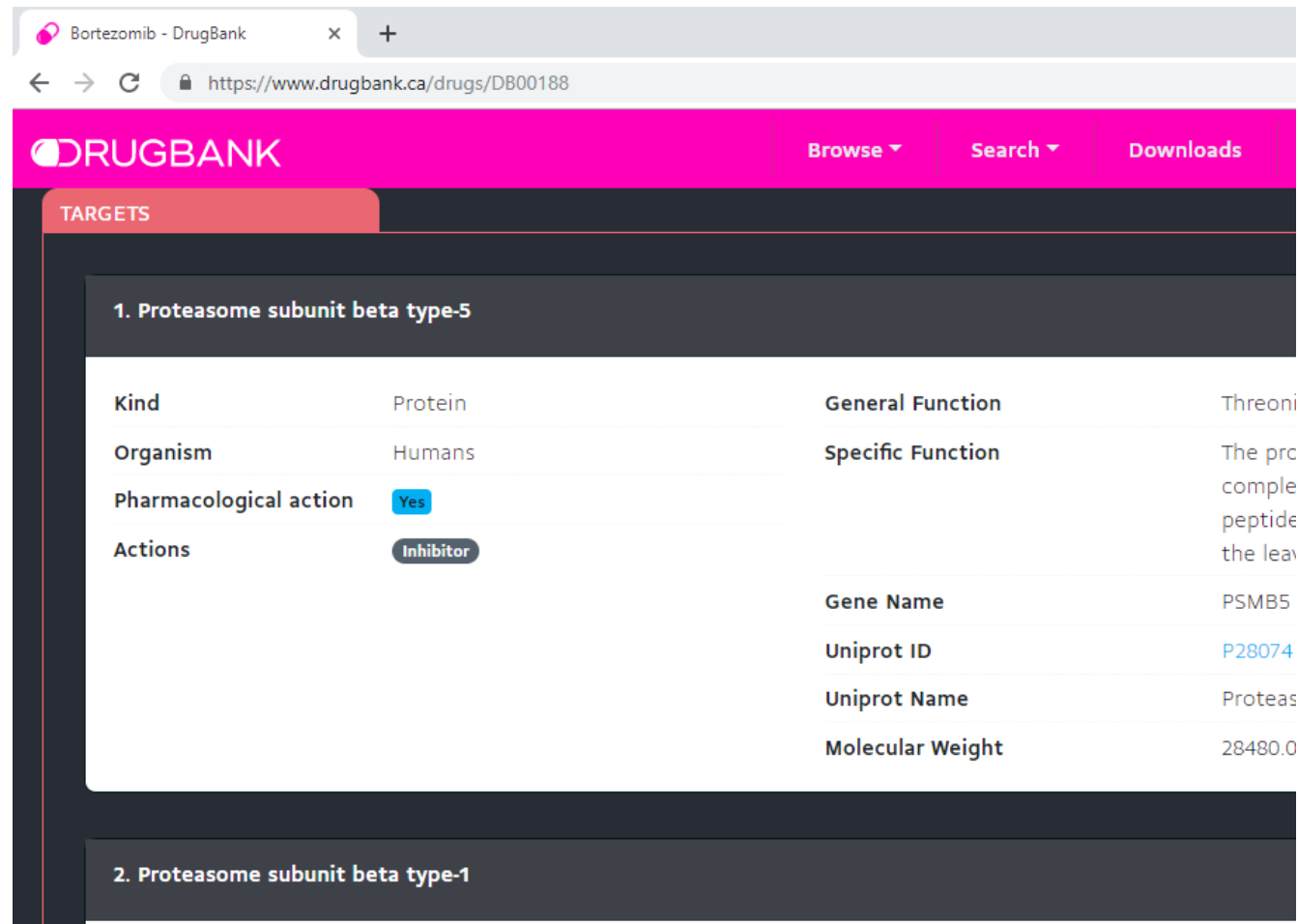
Matthew H. Bailey^{1, 2, 31}, Collin Tokheim^{3, 4, 31}, Eduard Porta-Pardo^{5, 6, 31}, Sohini Sengupta^{1, 2}, Denis Bertrand⁷, Amila Weerasinghe^{1, 2}, Antonio Colaprico^{8, 9, 10}, Michael C. Wendl^{2, 11, 12}, Jaegil Kim¹³, Brendan Reardon^{13, 14}, Patrick Kwok-Shing Ng¹⁵, Kang Jin Jeong¹⁶, Song Cao^{1, 2}, Zixing Wang¹⁷, Jianjiong Gao¹⁸, Qingsong Gao^{1, 2}, Fang Wang¹⁷, Eric Minwei Liu¹⁹ ... Li Ding^{1, 2, 12, 30, 32} ✉

General approach and data sources



How did we choose the drug targets?

- We considered the DrugBank database, due to its comprehensiveness and expert-curation
- Note that DrugBank is not tissue-specific



Bortezomib - DrugBank

https://www.drugbank.ca/drugs/DB00188

DRUGBANK

Browse Search Downloads

TARGETS

1. Proteasome subunit beta type-5

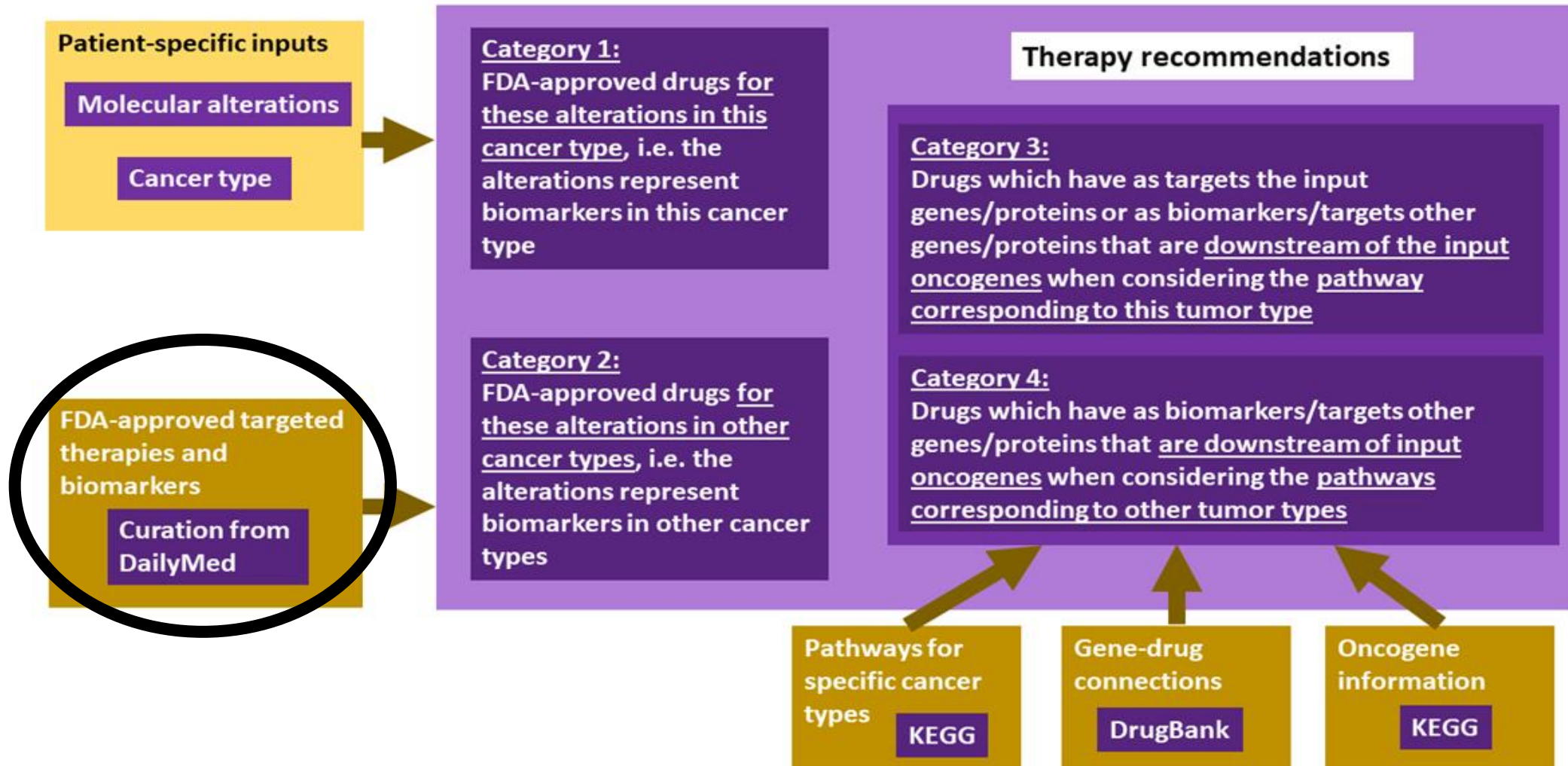
Kind	Protein	General Function	Threoni
Organism	Humans	Specific Function	The pro comple peptide the leav
Pharmacological action	Yes		
Actions	Inhibitor		
		Gene Name	PSMB5
		Uniprot ID	P28074
		Uniprot Name	Proteas
		Molecular Weight	28480.0

2. Proteasome subunit beta type-1

How did we choose the drug targets?

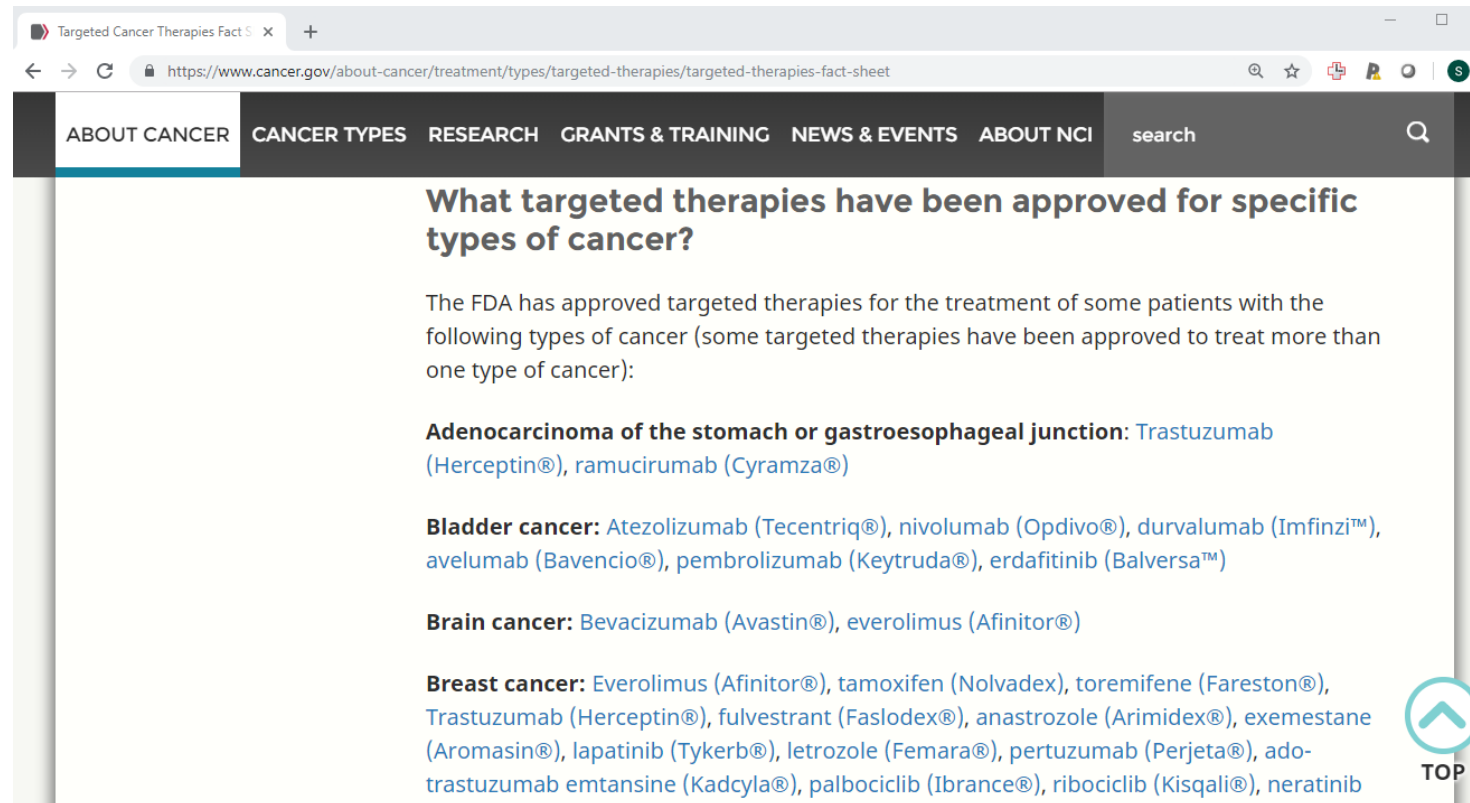
- We considered the DrugBank database, due to its comprehensiveness and expert-curation
- Note that DrugBank is not tissue-specific
- We downloaded all of DrugBank and read in the data, but will look into the ChemmineDrugs and paxtoolsr packages for the next iteration of our tool

General approach and data sources



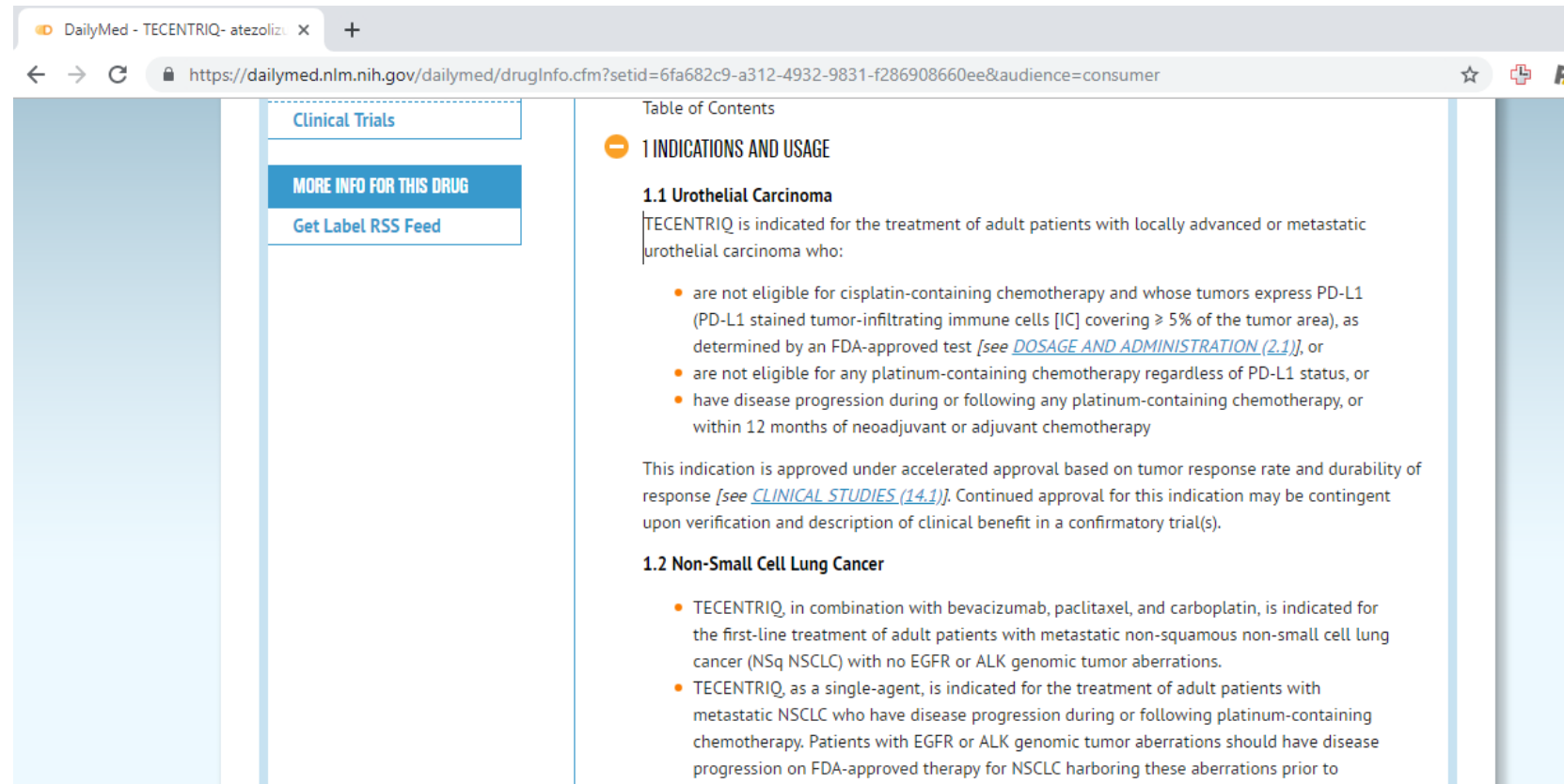
How did we obtain the FDA-approved targeted therapies and biomarkers?

- We performed manual curation of targeted cancer therapies:
 - We first got the **list of targeted therapies from the NCI**:



How did we obtain the FDA-approved targeted therapies and biomarkers?

- We performed manual curation of targeted cancer therapies:
 - We first got the list of targeted therapies from the NCI
 - We then followed the links to get to the **drug labels**, which are available through **NLM's DailyMed** and curated the therapy, biomarker, disease from the section “Indications and Usage”:



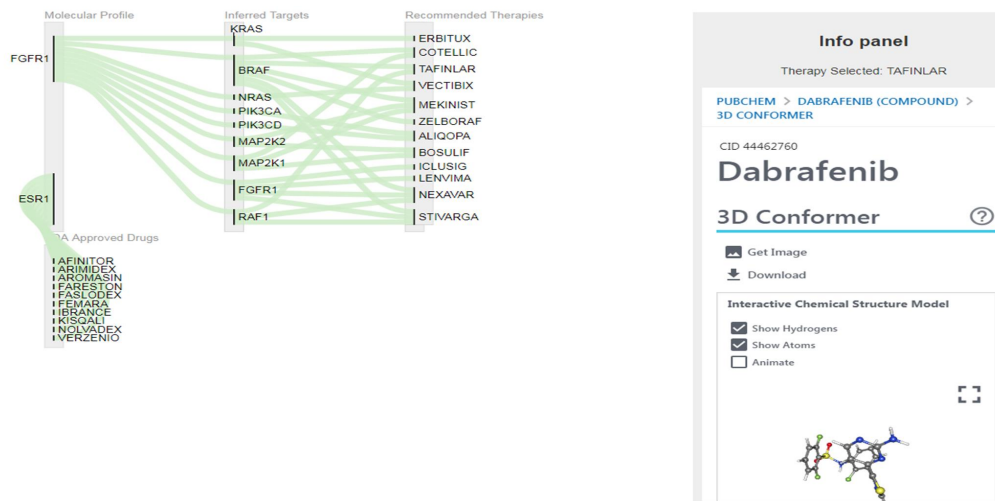
The screenshot shows a web browser window with the URL <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6fa682c9-a312-4932-9831-f286908660ee&audience=consumer>. The page title is "DailyMed - TECENTRIQ- atezolizumab". The left sidebar contains links for "Clinical Trials", "MORE INFO FOR THIS DRUG", and "Get Label RSS Feed". The main content area is titled "Table of Contents" and lists "1 INDICATIONS AND USAGE". Under "1.1 Urothelial Carcinoma", it states: "TECENTRIQ is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:" followed by a bulleted list of criteria: "are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test [see [DOSAGE AND ADMINISTRATION \(2.1\)](#)], or are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy". A paragraph follows: "This indication is approved under accelerated approval based on tumor response rate and durability of response [see [CLINICAL STUDIES \(14.1\)](#)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).". Under "1.2 Non-Small Cell Lung Cancer", it states: "TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations." and "TECENTRIQ, as a single-agent, is indicated for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to".

How did we obtain the FDA-approved targeted therapies and biomarkers?

- We performed manual curation of targeted cancer therapies:
 - We first got the of targeted therapies list from the NCI
 - We then followed the links to get to the drug labels, which are available through NLM's DailyMed and curated the therapy, biomarker, disease from the section "Indications and Usage"
- Clearly this **does not scale up well** for maintaining our tool, especially given the large number of recent approvals
- Databases exist with some of this information, but they were either difficult to use or had restrictive permissions
- Currently developing a package to do at least some preliminary curation via **natural language processing on the DailyMed API**

Relevant links

- 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)
- Preprint available at <https://www.biorxiv.org/content/10.1101/605261v1> (Kancherla, Rao et al)

Future development goals

- Categorize therapies by therapy classes, approval type etc, to rank them within categories and reduce the number of disjoint recommendations
- Consider other pathways besides KEGG, potentially allow users to upload their own set of pathways
- Automate more of the current steps
- Drill deeper into 1-2 different cancer types

Thank you!

Email me at:

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