GULBENKIAN CIÊNCIA

PO: Precision Oncology Course

Running PanDrugs

BU CNIO BIOINFORMATICS UNIT

cnio stop cancer

PanDrugs

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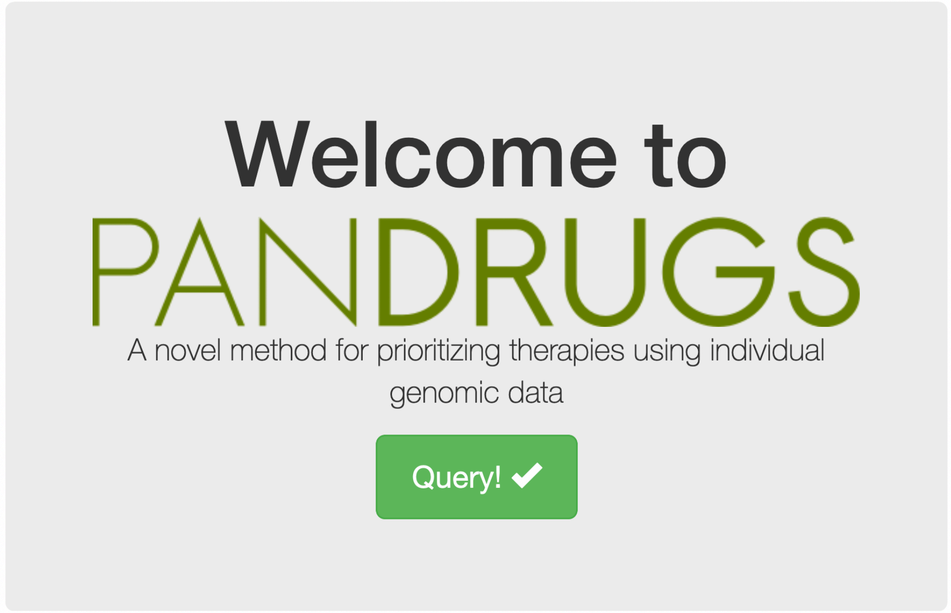
www.pandrugs.org



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PanDrugs is a web tool for **prioritizing cancer therapies** based on **individual genomics data**.

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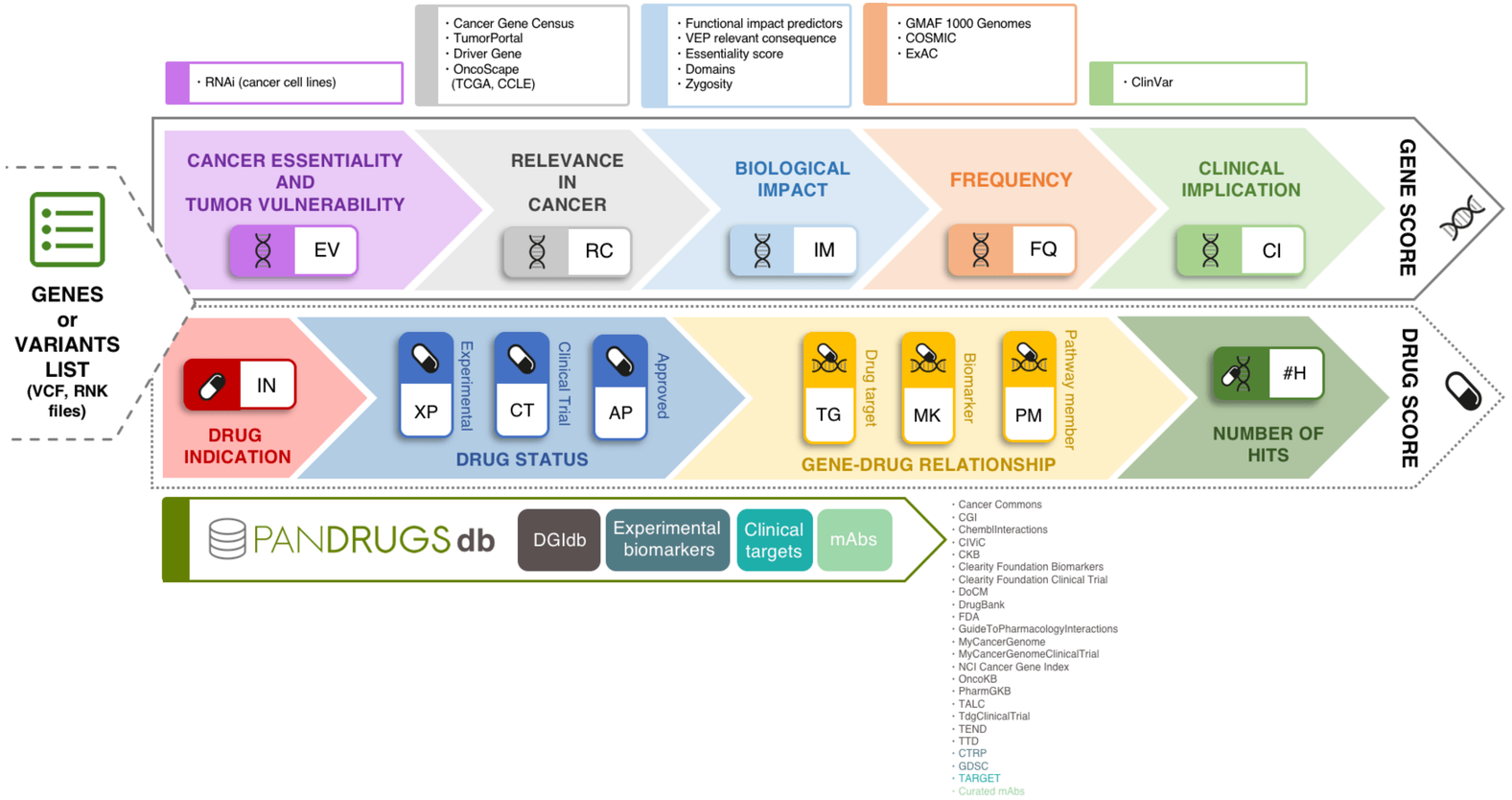
- **GScore (0 to 1):** Measures the **relevance of genetic variants in cancer**.
- **DScore (-1 to 1):** Measures the **drug efficacy** against different targets.



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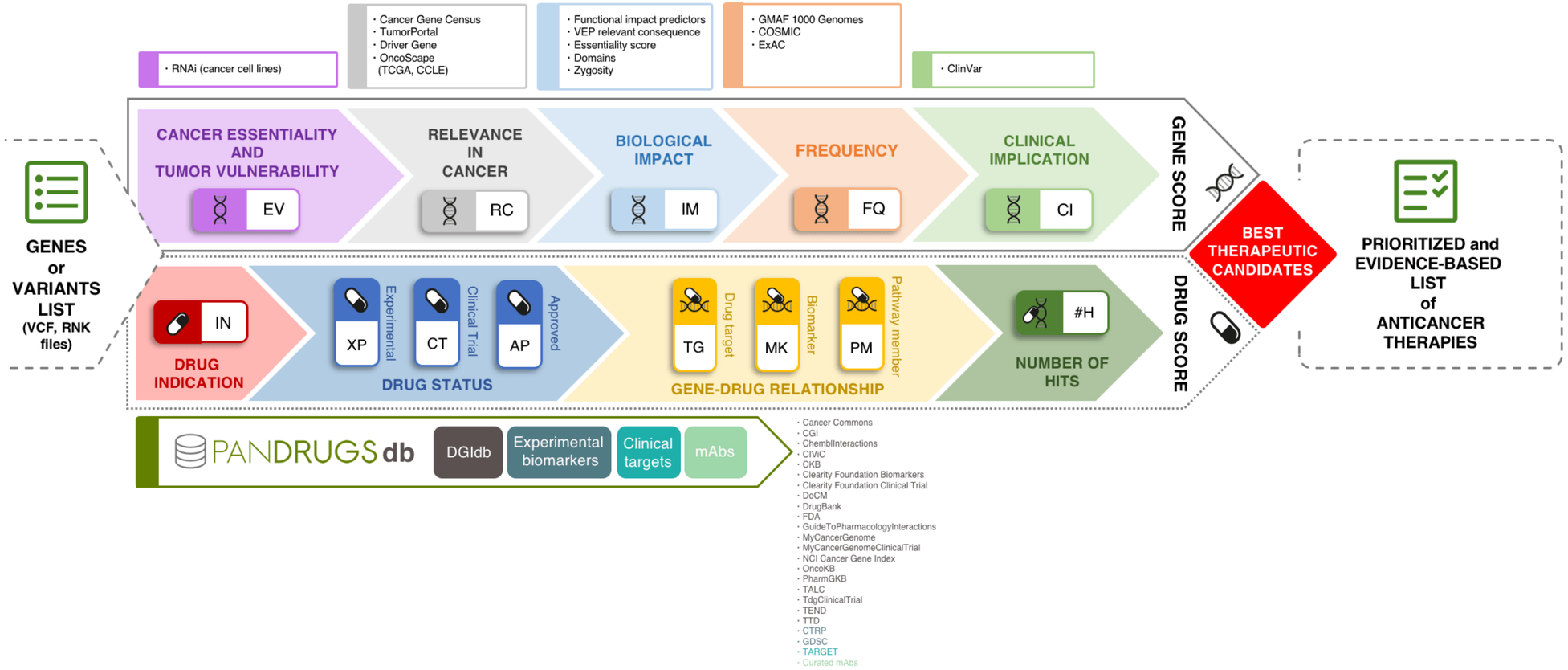
Based on these two scores, PanDrugs outputs a ranking of the **best therapeutic candidates** for a particular patient.



Input 1: Gene list

PANDRUGS

Steps

1. **Query PanDrugs using the Genes section**
2. **Load Example 3 (Genes Involved in PI3K-AKT-mTOR pathway)**
3. **Query the database with these genes**

Questions

PANDRUGS

Input 1: Gene list

- **Are all the genes in PanDrugs? How many drugs are in each approval status?**
- **Which is the most abundant mechanism of action?**
- **How can we find the best therapeutic candidates?**
- **Where are the evidences for these best therapeutic candidates?**
- **Is there any drug suggested by a gene that is discarded by another?**

Answers

PANDRUGS

Input 1: Gene list

- **Genes in PanDrugs: 17/17. Approval status: 120 approved, 175 in clinical trials and 360 experimental drugs**
- **Most abundant MoA: Serine/Threonine kinases**
- **Best therapeutic candidates: They appear in the green part of the plot and marked with a star in the table**
- **Evidences: Press “+” to expand an entry and check the PubMed and ClinicalTrials.org links to find the source of each relationship**
- **Drug suggested by a gene and discarded by another: Marked with a “!” or the label “Both”**

Input 2: Gene ranking

PANDRUGS

Steps

1. **Query PanDrugs using the Gene Ranking section**
2. **Load Example file (Expression data for the top 500 up-regulated genes in a lung adenocarcinoma patient with *EGFR* alteration from TCGA)**
3. **Query the database with these genes**

Questions

PANDRUGS

Input 2: Gene ranking

- **How many genes are in PanDrugs?**
- **Which are the best candidates according to PanDrugs?**
- **What are the evidences for the drugs that rank higher in the assignments?**
- **Is there any drug approved for the same cancer type?**

Answers

PANDRUGS

Input 2: Gene ranking

- **How many genes are in PanDrugs? 114**
- **Which are the best candidates according to PanDrugs? None**
- **What are the evidences for the drugs that rank higher in the assignments? Press “+” for Vorinostat, Paclitaxel and Bortezomib**
- **Is there any drug approved for the same cancer type? e.g. Paclitaxel, Pemetrexed and Gemcitabine. You can rerun PanDrugs selecting just “Lung” to filter out drugs with no evidence in lung**

Input 3: VCF

Steps

PANDRUGS

1. **Query PanDrugs using the Genomic Variant section**
2. **Load Example file (VCF of melanoma patient with mutant *BRAF* from TCGA)**
3. **Query the database with this file**

Questions

PANDRUGS

Input 3: VCF

- **Which are the suggested therapies? Do they match the specific alterations?**
- **What are the evidences for the gene with the highest GScore in the first best therapeutic candidate?**
- **Is there any drug suggested by a gene that is discarded by another?**
- **Is there any drug approved for the same cancer type? Is there any drug in cancer clinical trials for this cancer type?**
- **Could a drug repositioning approach be used?**

Answers

PANDRUGS

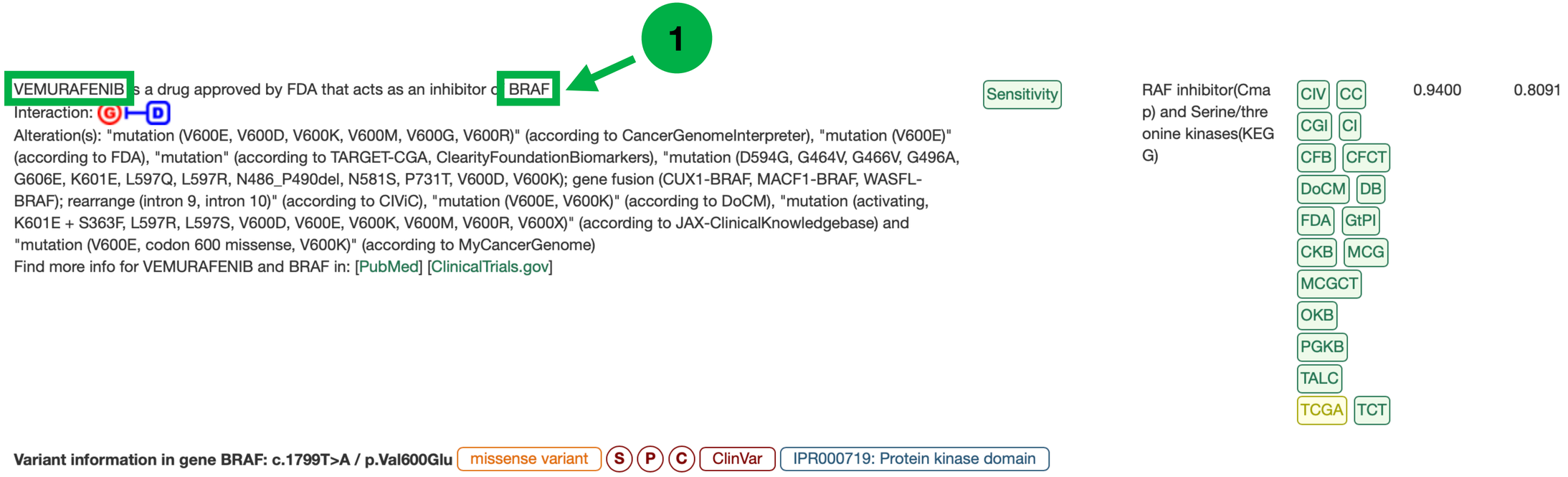
Input 3: VCF

- **Therapy and alterations:** In the table, if you press “+” you’ll see the variant-drug associations for the variants in the VCF
- **Highest GScore of the 1st BTC:** *BCL2* in Bortezomib. Click in the links for further information
- **Drug suggested and discarded by different genes:** e.g. Paclitaxel
- **Approved drug for the same cancer type:** Vemurafenib. **In clinical trials:** Not specified
- **Could a drug repositioning approach be used?** Yes, but Vemurafenib seems the best option

Answers

Therapy and alterations

If you expand a table row pressing “+” you’ll get info por a particular drug-gene pair 1.



Answers

PANDRUGS

Therapy and alterations

In some entries you have information about sensitivity/resistance (2) associated variants (3).

(2)

VEMURAFENIB is a drug approved by FDA that acts as an inhibitor of BRAF
Interaction:

Sensitivity

(3)

Alteration(s): "mutation (V600E, V600D, V600K, V600M, V600G, V600R)" (according to CancerGenomeInterpreter), "mutation (V600E)" (according to FDA), "mutation" (according to TARGET-CGA, ClearityFoundationBiomarkers), "mutation (D594G, G464V, G466V, G496A, G606E, K601E, L597Q, L597R, N486_P490del, N581S, P731T, V600D, V600K); gene fusion (CUX1-BRAF, MACF1-BRAF, WASFL-BRAF); rearrange (intron 9, intron 10)" (according to CIViC), "mutation (V600E, V600K)" (according to DoCM), "mutation (activating, K601E + S363F, L597R, L597S, V600D, V600E, V600K, V600M, V600R, V600X)" (according to JAX-ClinicalKnowledgebase) and "mutation (V600E, codon 600 missense, V600K)" (according to MyCancerGenome)
Find more info for VEMURAFENIB and BRAF in: [PubMed] [ClinicalTrials.gov]

RAF inhibitor(Cmap) and Serine/threonine kinases(KEGG)	CIV CC CGI CI CFB CFCT DoCM DB FDA GtPI CKB MCG MCGCT OKB PGKB TALC TCGA TCT	0.9400	0.8091

Variant information in gene BRAF: c.1799T>A / p.Val600Glu missense variant S P C ClinVar IPR000719: Protein kinase domain

Answers

PANDRUGS

Therapy and alterations

Below you have the variant(s) found in your VCF for that gene 4.

VEMURAFENIB is a drug approved by FDA that acts as an inhibitor of BRAF Interaction: G⊣D Alteration(s): "mutation (V600E, V600D, V600K, V600M, V600G, V600R)" (according to CancerGenomeInterpreter), "mutation (V600E)" (according to FDA), "mutation" (according to TARGET-CGA, ClearityFoundationBiomarkers), "mutation (D594G, G464V, G466V, G496A, G606E, K601E, L597Q, L597R, N486_P490del, N581S, P731T, V600D, V600K); gene fusion (CUX1-BRAF, MACF1-BRAF, WASFL-BRAF); rearrange (intron 9, intron 10)" (according to CIViC), "mutation (V600E, V600K)" (according to DoCM), "mutation (activating, K601E + S363F, L597R, L597S, V600D, V600E, V600K, V600M, V600R, V600X)" (according to JAX-ClinicalKnowledgebase) and "mutation (V600E, codon 600 missense, V600K)" (according to MyCancerGenome) Find more info for VEMURAFENIB and BRAF in: [PubMed] [ClinicalTrials.gov]	Sensitivity	RAF inhibitor(Cmap) and Serine/threonine kinases(KEGG)	CIV CC CGI CI CFB CFCT DoCM DB FDA GtPI CKB MCG MCGCT OKB PGKB TALC TCGA TCT	0.9400	0.8091

Variant information in gene BRAF: c.1799T>A / p.Val600Glu missense variant S P C ClinVar IPR000719: Protein kinase domain

4

Answers

PANDRUGS

Therapy and alterations

In this case, our *BRAF* variant (p.Val600Glu or V600E) is associated with sensitivity to VEMURAFENIB according to CancerGenomeInterpreter, FDA, DoCM, JAX-ClinicalKnowledgebase and MyCancerGenome.

VEMURAFENIB is a drug approved by FDA that acts as an inhibitor of BRAF Interaction: G⊣D Alteration(s): "mutation (V600E, V600D, V600K, V600M, V600G, V600R)" (according to CancerGenomeInterpreter), "mutation (V600E)" (according to FDA), "mutation" (according to TARGET-CGA, ClearityFoundationBiomarkers), "mutation (D594G, G464V, G466V, G496A, G606E, K601E, L597Q, L597R, N486_P490del, N581S, P731T, V600D, V600K); gene fusion (CUX1-BRAF, MACF1-BRAF, WASFL-BRAF); rearrange (intron 9, intron 10)" (according to CIViC), "mutation (V600E, V600K)" (according to DoCM), "mutation (activating, K601E + S363F, L597R, L597S, V600D, V600E, V600K, V600M, V600R, V600X)" (according to JAX-ClinicalKnowledgebase) and "mutation (V600E, codon 600 missense, V600K)" (according to MyCancerGenome) Find more info for VEMURAFENIB and BRAF in: [PubMed] [ClinicalTrials.gov]	Sensitivity	RAF inhibitor(Cmap) and Serine/threonine kinases(KEGG)	CIV CC CGI CI CFB CFCT DoCM DB FDA GtPI CKB MCG MCGCT OKB PGKB TALC TCGA TCT	0.9400	0.8091

Variant information in gene BRAF: c.1799T>A / p.Val600Glu missense variant S P C ClinVar IPR000719: Protein kinase domain

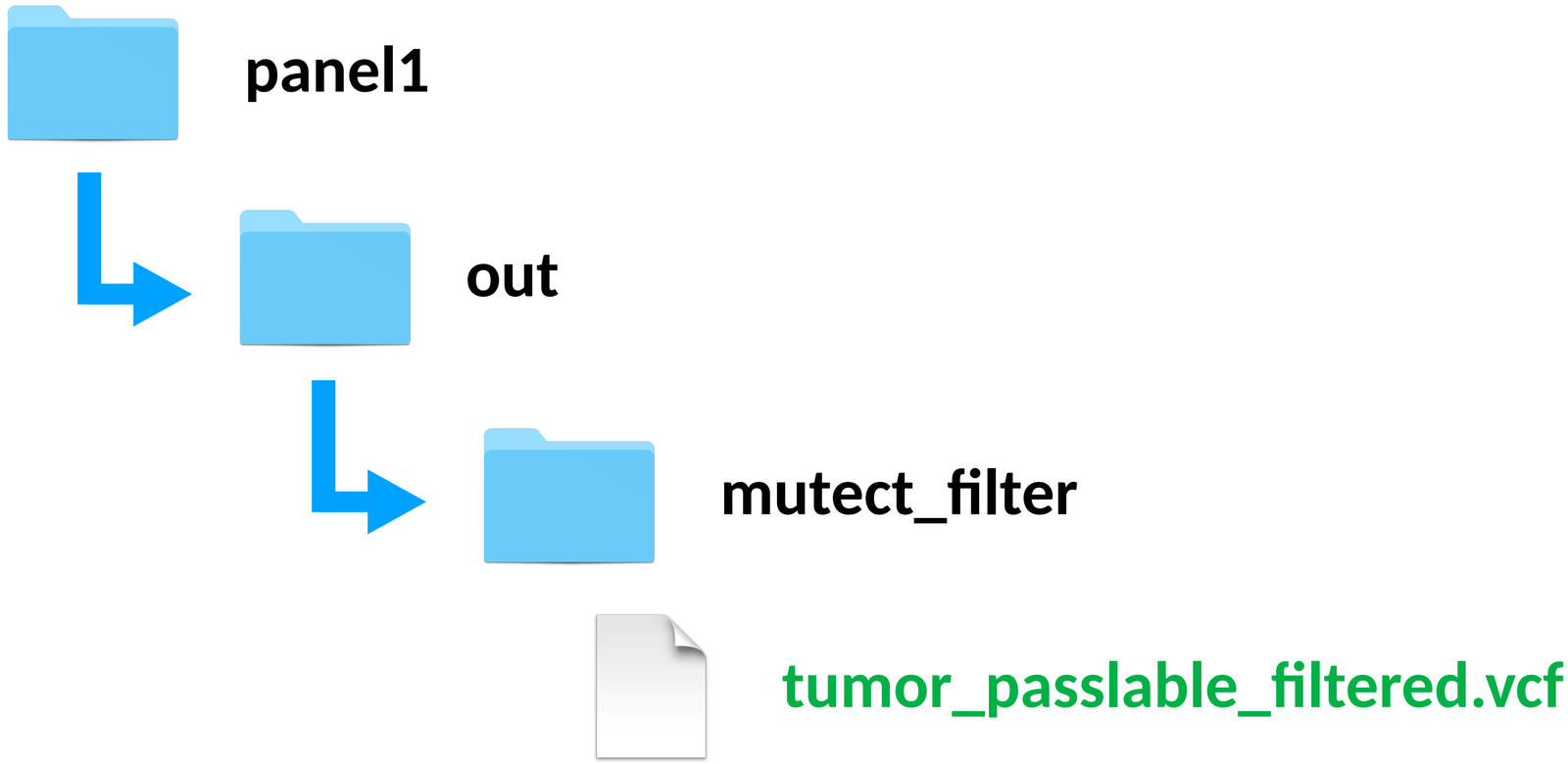
Input 4: VCF

Steps

PANDRUGS

1. **Query PanDrugs using the Genomic Variant section**
2. **Load the VCF without annotations from the exercise of the CHP patient**
3. **Query the database with this file**

Input 4: VCF



Data: https://drive.google.com/file/d/1BknV7nyQDrUJ6LgAxh4ln8qVriUNI8-F/view?usp=sharing

Questions

PANDRUGS

Input 4: VCF

- **Which are the suggested therapies?**
- **Is there any drug suggested by a gene that is discarded by another?**
- **Is there any drug approved for the same cancer type? Is there any drug in cancer clinical trials for this cancer type?**
- **Could a drug repositioning approach be used?**

Answers

PANDRUGS

Input 4: VCF

- **Which are the suggested therapies? The BTC marked with a star**
- **Drug suggested and discarded by different genes: e.g. Regorafenib (“Both”) or Trametinib (“!”)**
- **Approved drug for the same cancer type: Regorafenib is approved for colon. In clinical trials: Not specified**
- **Drug repositioning: Trametinib (skin cancer) could be used because the patient has a variant in *PIK3CA* (p.His1047Arg) associated to sensitivity to this drug. Also, they don’t show any of the variants in *MAP2K1* associated with resistance to Trametinib.**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Thanks!


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