

# PredictSNP<sup>ONCO</sup>: A Web Server for Rapid Structural Bioinformatics Analysis of the Effect of Cancer-associated Mutations

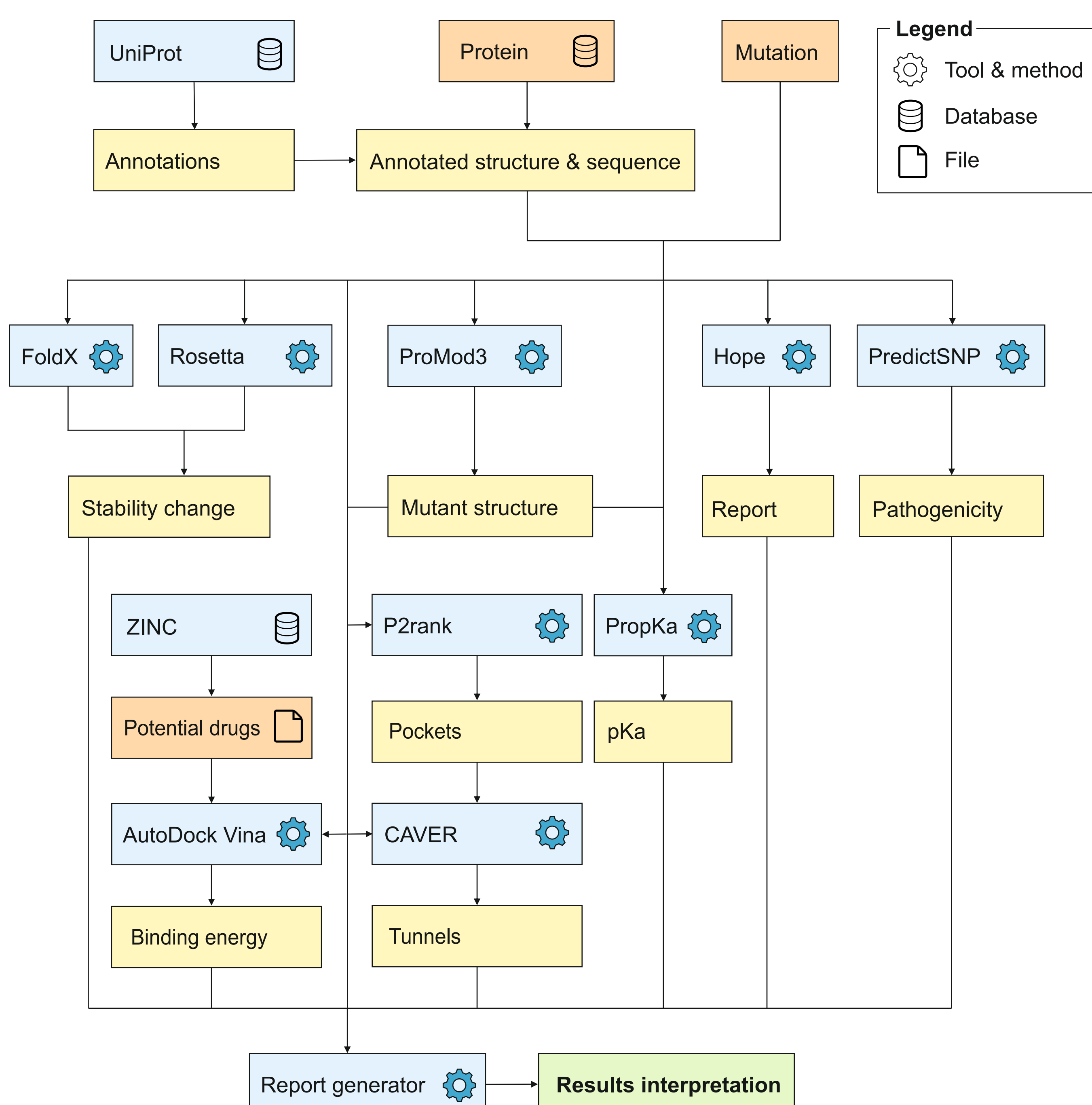
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## INTRODUCTION

Despite significant recent improvements in pediatric oncology, the success rate for the treatment of certain malignancies remains challenging [1]. Therefore, there is a great demand for novel approaches such as precision oncology, which breaks the traditional "one-size-fits-all" paradigm and tries to deliver the right care to the right patient at the right time. It is based on the design of the most suitable therapeutic plan for each patient by the oncology experts in a very limited time frame. The experts have to evaluate a vast amount of data about the patients, their life and the tumor from the detailed molecular characterization and various bioinformatics analyses [2]. Even though this approach requires a lot of effort, it is used in many hospitals around the globe, demonstrating its positive impact [3-5]. This approach is also used in the Department of Children's Oncology of the University Hospital in Brno. Their data acquisition pipeline [6] is based on transcriptome sequencing of the tumor, followed by *in silico* analyses of identified mutations and changes in metabolic pathways. However, structural analysis is missing in the current pipeline. Therefore, structure-based prediction of the effect of mutations and evaluation of binding affinities of possible drugs is of great interest.

## WORKFLOW



## DECISION TREE

- Combination of data into a **single decision**
- Manual and machine-learning based trees**
- Experimentally validated datasets**
- Manual decision tree performance:
  - Accuracy: 80%
  - Sensitivity: 83%
  - Specificity: 66%
  - Precision: 93%

## EXAMPLE RESULTS



## OBJECTIVES & CHALLENGES

- The service must be **fully automatic** and should not need any user interactions
- The pipeline must provide **all relevant data** about the possible impact of mutation
- The calculations must be **highly parallel** and **executable on supercomputers** to achieve execution time less than 14 days because the Board needs to make the decision quickly
- All the results must be **presented in a comprehensive and straightforward way** using appropriate color coding and visual elements as the medical experts are not protein chemists
- The tool should be **easy to use** and must **not require any knowledge** about the studied proteins
- The tool must provide **interactive and user-friendly web interface** as multiple hospitals around the world can benefit from our analyses

## GRAPHICAL USER INTERFACE

**Summary for CDK4 K22A**

Impact - PredictSNP: Deleterious (Confidence: 76%)

Stability - FoldX: Deleterious (K22A: -1.6 kcal/mol)

Stability - Rosetta: Deleterious (K22A: 1.7 kcal/mol)

Mutation position: Non-essential residue in cytoplasmic domain

Catalytic residues: Changes in pKa (K35, D140)

Inhibitors: Changes in binding energy (0, 387, 2812, 1142, 80)

**Mutant description** (HOPE):

- There is a difference in charge between the wild-type and mutant amino acid.
- The charge of the wild-type residue is lost by this mutation. This can cause loss of interactions with other molecules.
- The wild-type and mutant amino acids differ in size.
- The mutant residue is smaller than the wild-type residue.
- This will cause a possible loss of external interactions.
- The hydrophobicity of the wild-type and mutant residue differs.

**3D visualization** (MolView): Open structure viewer showing the protein structure with the mutated position highlighted.

**Inhibitors** (show only associated drugs):

Database	Inhibitor Name	Wild Type kcal/mol	Mutant kcal/mol	Difference kcal/mol	Select In Chart
DB11730	ZINC72316335	-8	-9.3	-1.3	Select
DB12001	Abemaciclib	-8.3	-9.3	-1	Select
DB09073	Palbociclib	-8.7	-7.3	1.4	Select
DB12010	Fostamatinib	-8.1	-6.9	1.2	Select
DB08901	Ponatinib	-9	-10.6	-1.6	Select
ZINC1490477	Tolvaptan	-9.7	-10.3	-0.6	Select
DB09143	Erisimodigib	-9.1	-10.3	-1.2	Select
DB11363	Alectinib	-9.9	-10.3	-0.4	Select

## REFERENCES

- Steliarova-Foucher, E., Stiller, C., Kaatsch, P., Berrino, F., Coebergh, J.W., Lacour, B., Parkin, M., 2014: **Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study.** *Lancet* 364:2097-2105.
- Kalia, M., 2013: **Personalized oncology: recent advances and future challenges.** *Metabolism* 62: S11-S14.
- Schwaederle, M., Parker, B.A., Schwab, R.B., Daniels, G.A., Piccioni, D.E., Kesari, S., Helsten, T.L., Bazhenova, L.A., Romero, J., Fanta, P.T., Lippman, S.M., Kurzrock, R., 2016: **Precision oncology: the UC San Diego Moores Cancer Center PREDICT experience.** *Molecular Cancer Therapeutics* 15: 743-752.
- Wheler, J., Tsimberidou, A.M., Hong, D., Naing, A., Falchook, G., Piha-Paul, S., Fu, S., Moulder, S., Stephen, B., Wen, S., Kurzrock, R., 2012: **Survival of 1,181 patients in a phase I clinic: the MD Anderson Clinical Center for targeted therapy experience.** *Clinical Cancer Research* 18: 2922-2929.
- Kris, M.G., Johnson, B.E., Berry, L.D., Kwiatkowski, D.J., Iafrate, A.J., Wistuba, I.I., Varella-Garcia, M., Franklin, W.A., Aronson, S.L., Su, P.F., Shyr, Y., Camidge, D.R., Sequist, L.V., Glisson, B.S., Khuri, F.R., Garon, E.B., Pao, W., Rudin, C., Schiller, J., Haura, E.B., Socinski, M., Shirai, K., Chen, H., Giaccone, G., Ladanyi, M., Kugler, K., Minna, J.D., Bunn, P.A., 2014: **Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs.** *Journal of the American Medical Association* 31119: 1998-2006.
- Benzekry, S., Tuszynski, J.A., Rietman, E.A., Klement, G.L., 2015: **Design principles for cancer therapy guided by changes in complexity of protein-protein interaction networks.** *Biology Direct* 10: 32.

