# NextDOM 2.0: Detector of Somatic Point Mutations in Leukemias Resistant to Therapy

Pavla Suchánková1, Adéla Benešová1, Pavla Pecherková1, 2, Václava Polívková1, Jitka Koblihová1,

Kateřina Machová Polaková1, 3

*1 Institute of Hematology and Blood Transfusion, Prague, Czech Republic*

*2 Faculty of Transportation Sciences, Czech Technical University, Prague, Czech Republic*

*3 Institute of Pathological Physiology, 1st Medicine Faculty, Charles University, Prague, Czech Republic*

Chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (Ph+ ALL) are diseases associated with a characteristic chromosomal translocation called the Philadelphia chromosome. This chromosomal abnormality generates the fusion gene encoding BCR::ABL1 oncoprotein. The development of mutations in the kinase domain (KD) of BCR::ABL1 is a known mechanism leading to the resistance to CML and Ph+ ALL treatment, therefore early and correct mutation detection is crucial for better disease management.

Next-generation sequencing (NGS) of the targeted region of BCR::ABL1 KD enables to detect point mutations at very low-levels. In common practice, universal thresholds for mutation calling are used (most frequently 5% or 3%), which can lead to false negative or false positive results. Therefore, for precise variant calling and correct error detection, it is necessary to set individual thresholds for each sequenced position.

The NextDOM Set of Thresholds Creator calculates the individual threshold level for each sequenced position individually. This Set of Thresholds calculation uses NGS data from samples of healthy donors expecting no somatic point mutations. The appropriate thresholds are calculated only for positions that meet the criteria for a data quality control (number of pair reads). NextDOM applies this Set of Thresholds to NGS data of the patient sample and reports the mutations at statistically significant levels. The program also reports about clinical relevance of significant variants using the up-loaded list of the mutations which have been published in connection with resistance to therapy.

The NextDOM Set of Thresholds Creator can be used as a universal thresholds calculator and the NextDOM is modifiable for determining relevant mutation detection in various amplicon sequencing data.