Why?

Very low frequency mutation in specific cancer type may have deep functional impact (in metabolism?).

These cancer-specific liabilities may enable finding synthetically lethal target (in metabolism?).

Cancer patients at MSKCC receive routinely genetic profiling. Identifying those few patients with the very low frequency mutation can provide a unique therapeutic opportunity.

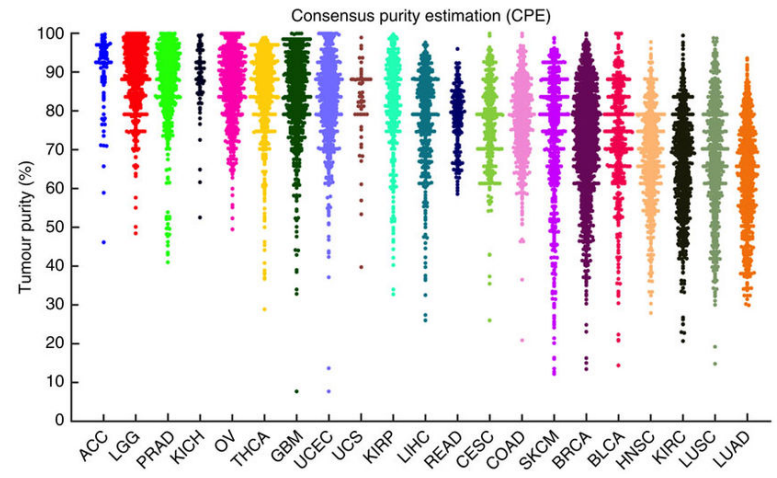
Concerns

How low can we go before drug dvlp is unfeasible?

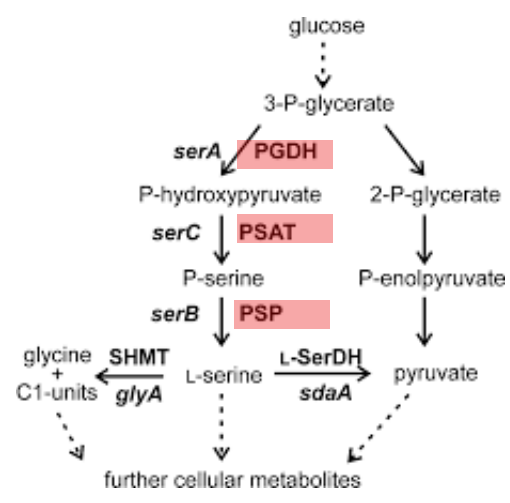
How to get consistent genetic signature of the mutation?

Get mutation data from 33 cancers

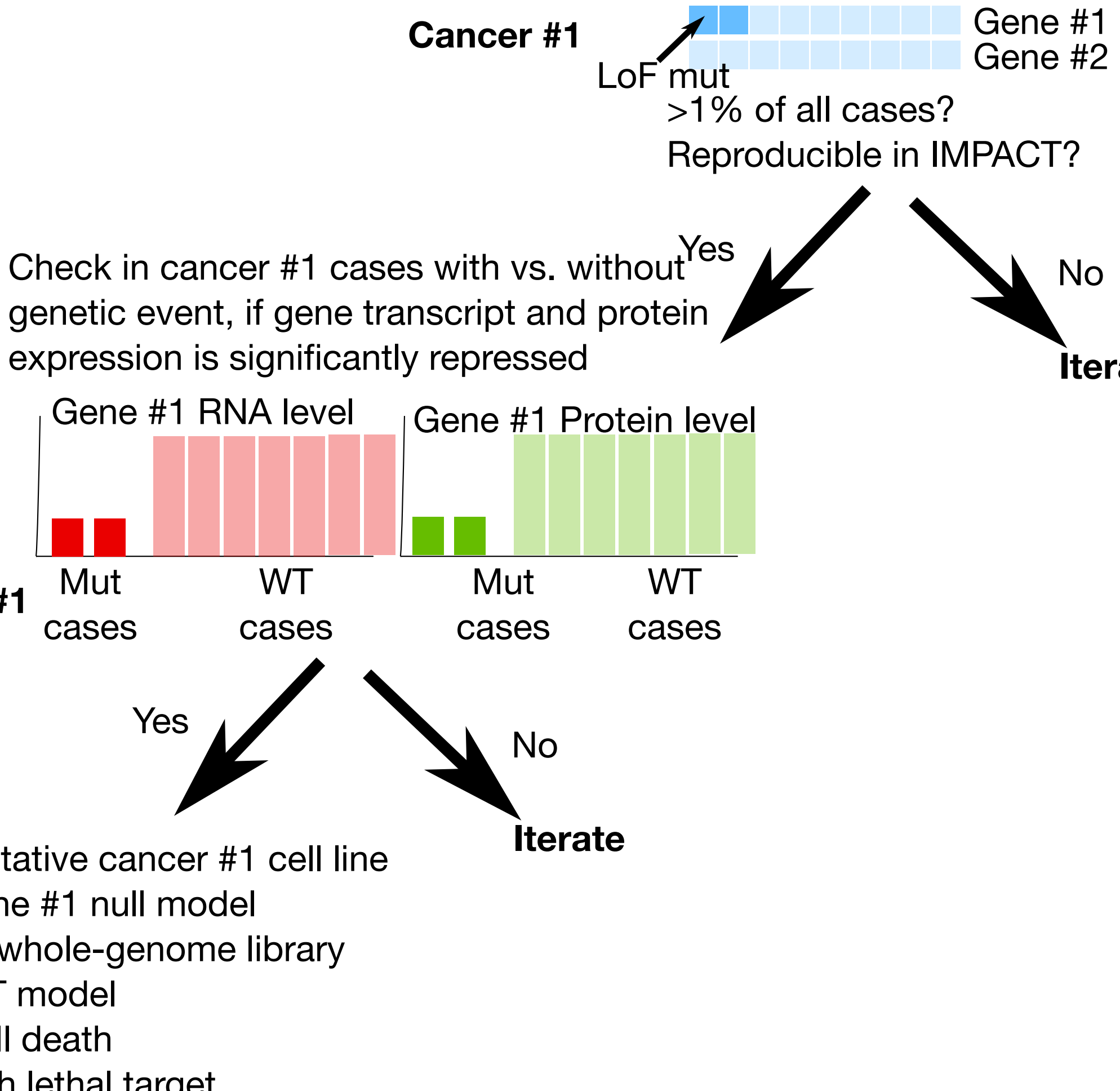
Sort cancer by tumor purity



Retrieve all univocal rxn-encoding genes from HMR2



Starting from cancer #1, check high impact loss-of-function or deletion for each gene



Get representative cancer #1 cell line

Generate gene #1 null model

CRISPR out whole-genome library in null vs. WT model

Select for cell death

Validate synth lethal target