**Proposed goal of paper E**

1. Provide uniform functional annotations for germline and somatic variants
2. Utilize these functional annotations to evaluate functional burdening of germline and somatic genomes across pan-cancer dataset.
   1. Impact of genomic variation on TF binding sites (gain & loss of TF motifs)
   2. Impact of genomic variation on promoter and enhancer region

3) Relating functional burdening with other genomic signatures

Replication timing, histone marks and mutation signatures

4) Relating functional burdening for samples where gene expression data is available

**Proposed Analyses for the functional impact paper**

functional impact of SNVs/Indels

FunSeq based scoring scheme

Comparing functional impact of germline and somatic mutations

Impact of SNVs on TF binding motifs

Landscape of TFBS alterations over all cancer types

kinases

Functional impact of mutations in protein kinases

functional impact of SVs

Scoring impact of large SV and CNVs in germline and cancer genome

latent driver

Identifying latent-driver(“deleterious” passenger) based on functional impact score

Identifying passenger mutations leading to differential gene expression based on RNA-Seq data

Quantifying negative selection

Closely looking at essential genes

aggregating statistics over given functional element( promoter, enhancer, ncRNA)

functional impact measure