

**S1 Method. Basic somatic/germline prediction comparator method.** As suggested by Jones et al. 2015, the tumor-cellularity-based algorithm uses the fraction of mutational allele and the sample purity alone to distinguish germline from somatic mutations. Briefly, for a mutation with allele frequency  $f$  and depth  $n$  from a sample with purity  $p$ : 1) if  $f > 0.95$  and  $p < 0.90$ , the mutation is reported as germline. If  $p > 0.9$ , it's classified as ambiguous due to high tumor content; 2) if  $f < 0.95$ , a binomial test is performed to assess the probability of mutational allele to be  $nf$  or further from  $0.5f$ , which is the p-value. If p-value  $< 0.05$ , the mutation will be reported as somatic and germline otherwise. The following flowchart visually shows the implementation of the basic tumor-cellularity-based algorithm to which we compare somatic/germline classification performance.

