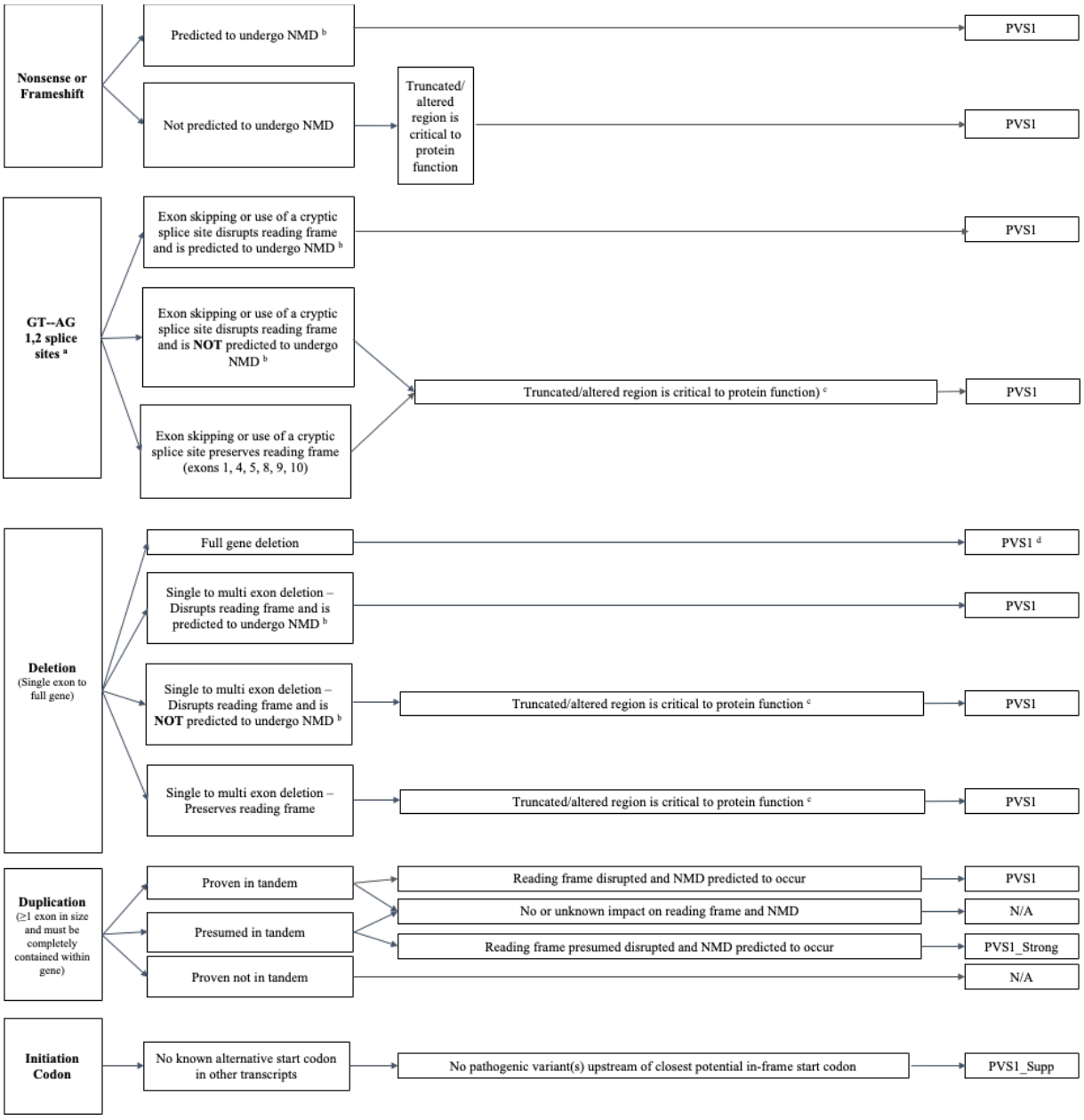
GCK PVS1 Decision Tree (Adapted from PMID: 30192042)



(a) This criterion should not be applied in combination with in silico splicing predictions (PP3). Additionally, splice site variants must have no detectable nearby (+/- 20 nts) strong consensus splice sequence that may reconstitute in-frame splicing. (b) NMD prediction based on the premature termination codon not occurring in the 3' most exon or the 3'-most 50 bp of the penultimate exon. (c) Relevant domain indicated by experimental evidence proving a critical role of the domain and/or presence of non-truncating pathogenic variants in the region. (d) Given that GCK is a known haploinsufficient gene, a pathogenic classification is warranted for a full gene deletion (in the absence of conflicting data) even though application of PVS1 alone would not reach a pathogenic classification using the combining rules in Richards et al. (2015). NMD, nonsense-mediated decay; LoF, loss of function.