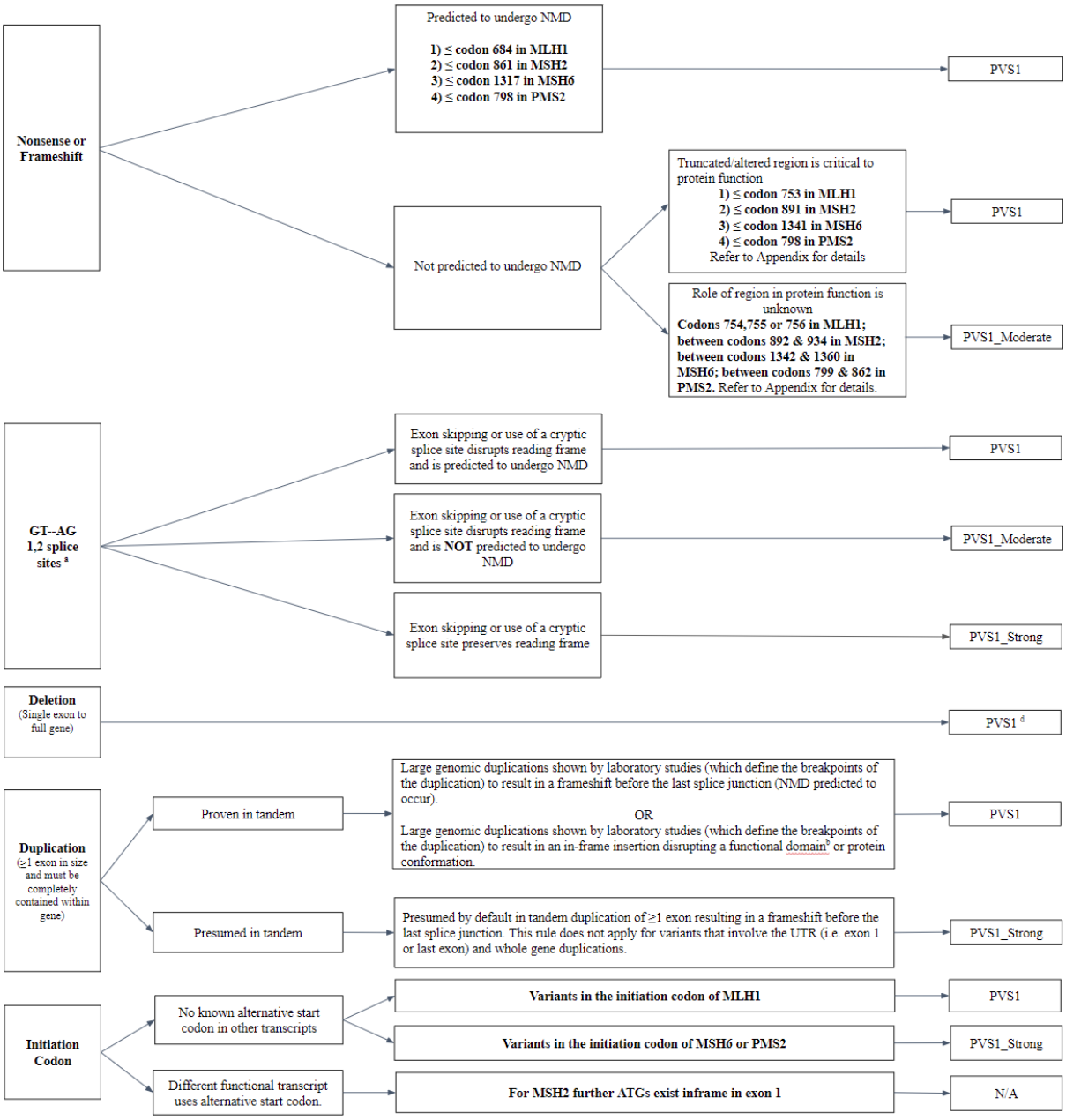
Nonsense or Frameshift
Predicted to undergo NMD
1) ≤ codon 684 in MLH1
2) ≤ codon 861 in MSH2
3) ≤ codon 1317 in MSH6
4) ≤ codon 798 in PMS2
PVS1
Not predicted to undergo NMD
Truncated/altered region is critical to protein function
1) ≤ codon 753 in MLH1
2) ≤ codon 891 in MSH2
3) ≤ codon 1341 in MSH6
4) ≤ codon 798 in PMS2
Refer to Appendix for details
PVS1
Role of region in protein function is unknown
Codons 754,755 or 756 in MLH1; between codons 892 & 934 in MSH2; between codons 1342 & 1360 in MSH6; between codons 799 & 862 in PMS2. Refer to Appendix for details.
PVS1_Moderate
GT--AG 1,2 splice sites [a]
Exon skipping or use of a cryptic splice site disrupts reading frame and is predicted to undergo NMD
PVS1
Exon skipping or use of a cryptic splice site disrupts reading frame and is NOT predicted to undergo NMD
PVS1_Moderate
Exon skipping or use of a cryptic splice site preserves reading frame
PVS1_Strong
Deletion
(Single exon to full gene)
PVS1 [d]
Duplication
(≥1 exon in size and must be completely contained within gene)
Proven in tandem
Large genomic duplications shown by laboratory studies (which define the breakpoints of the duplication) to result in a frameshift before the last splice junction (NMD predicted to occur).
OR
Large genomic duplications shown by laboratory studies (which define the breakpoints of the duplication) to result in an in-frame insertion disrupting a functional domain[b] or protein conformation.
PVS1
Presumed in tandem
Presumed by default in tandem duplication of ≥1 exon resulting in a frameshift before the last splice junction. This rule does not apply for variants that involve the UTR (i.e. exon 1 or last exon) and whole gene duplications.
PVS1_Strong
Initiation Codon
No known alternative start codon in other transcripts
Variants in the initiation codon of MLH1
PVS1
Variants in the initiation codon of MSH6 or PMS2
PVS1_Strong
Different functional transcript uses alternative start codon.
For MSH2 further ATGs exist inframe in exon 1
N/A