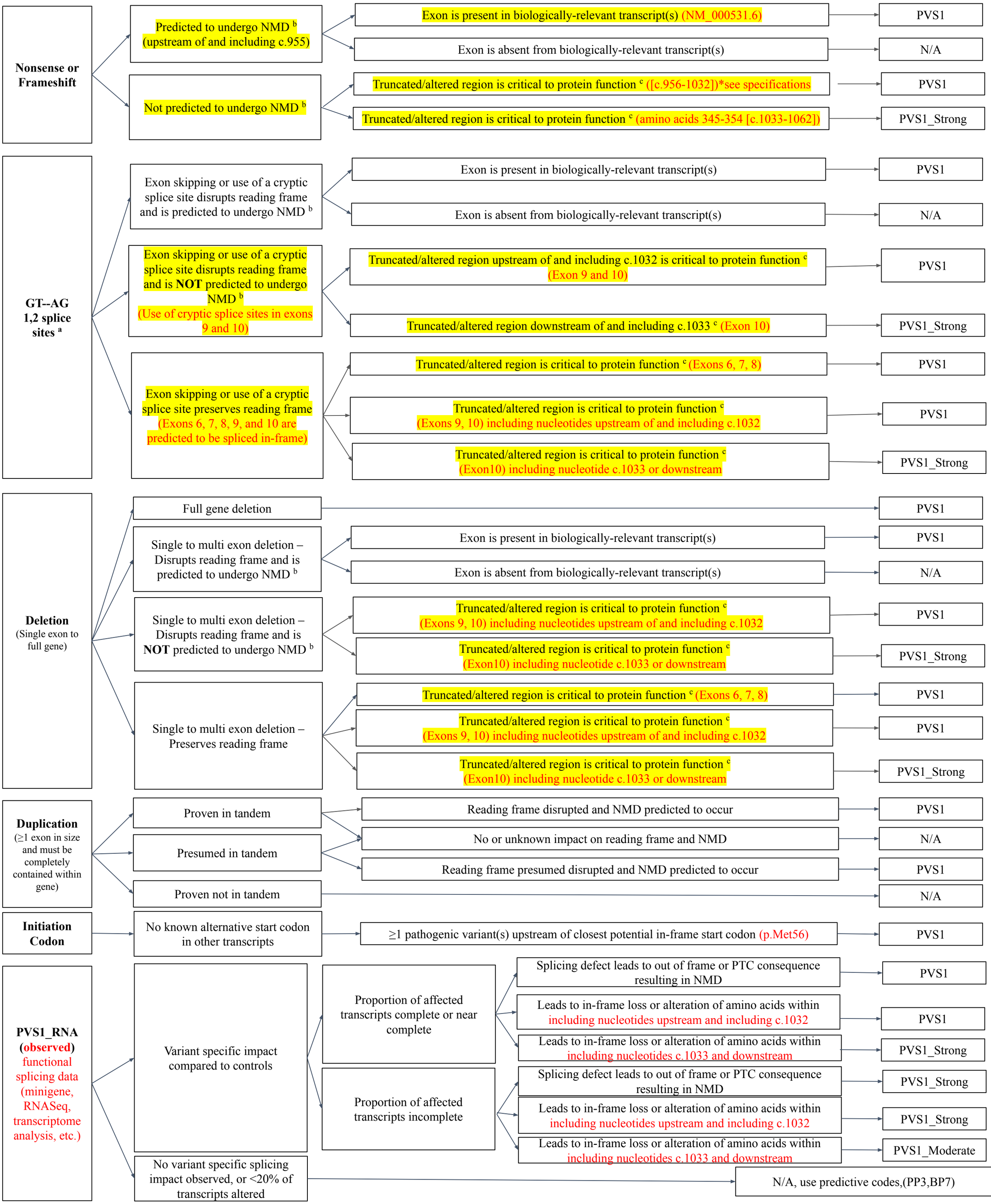
Nonsense or Frameshift
Predicted to undergo NMD b (upstream of and including c.955)
Exon is present in biologically-relevant transcript(s) (NM_000531.6)
PVS1
Exon is absent from biologically-relevant transcript(s)
N/A
Not predicted to undergo NMD b
Truncated/altered region is critical to protein function c ([c.956-1032])*see specifications
PVS1
Truncated/altered region is critical to protein function c (amino acids 345-354 [c.1033-1062])
PVS1_Strong
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 b
Exon is present in biologically-relevant transcript(s)
PVS1
Exon is absent from biologically-relevant transcript(s)
N/A
Exon skipping or use of a cryptic splice site disrupts reading frame and is NOT predicted to undergo NMD b (Use of cryptic splice sites in exons 9 and 10)
Truncated/altered region upstream of and including c.1032 is critical to protein function c (Exon 9 and 10)
PVS1
Truncated/altered region downstream of and including c.1033 c (Exon 10)
PVS1_Strong
Exon skipping or use of a cryptic splice site preserves reading frame (Exons 6, 7, 8, 9, and 10 are predicted to be spliced in-frame)
Truncated/altered region is critical to protein function c (Exons 6, 7, 8)
PVS1
Truncated/altered region is critical to protein function c (Exons 9, 10) including nucleotides upstream of and including c.1032
PVS1
Truncated/altered region is critical to protein function c (Exon10) including nucleotide c.1033 or downstream
PVS1_Strong
Deletion (Single exon to full gene)
Full gene deletion
PVS1
Single to multi exon deletion – Disrupts reading frame and is predicted to undergo NMD b
Exon is present in biologically-relevant transcript(s)
PVS1
Exon is absent from biologically-relevant transcript(s)
N/A
Single to multi exon deletion – Disrupts reading frame and is NOT predicted to undergo NMD b
Truncated/altered region is critical to protein function c (Exons 9, 10) including nucleotides upstream of and including c.1032
PVS1
Truncated/altered region is critical to protein function c (Exon10) including nucleotide c.1033 or downstream
PVS1_Strong
Single to multi exon deletion – Preserves reading frame
Truncated/altered region is critical to protein function c (Exons 6, 7, 8)
PVS1
Truncated/altered region is critical to protein function c (Exons 9, 10) including nucleotides upstream of and including c.1032
PVS1
Truncated/altered region is critical to protein function c (Exon10) including nucleotide c.1033 or downstream
PVS1_Strong
Duplication (≥1 exon in size and must be completely contained within gene)
Proven in tandem
Presumed in tandem
Reading frame disrupted and NMD predicted to occur
PVS1
No or unknown impact on reading frame and NMD
N/A
Reading frame presumed disrupted and NMD predicted to occur
PVS1
Proven not in tandem
N/A
Initiation Codon
No known alternative start codon in other transcripts
≥1 pathogenic variant(s) upstream of closest potential in-frame start codon (p.Met56)
PVS1
PVS1_RNA (observed) functional splicing data (minigene, RNASeq, transcriptome analysis, etc.)
Variant specific impact compared to controls
Proportion of affected transcripts complete or near complete
Splicing defect leads to out of frame or PTC consequence resulting in NMD
PVS1
Leads to in-frame loss or alteration of amino acids within including nucleotides upstream and including c.1032
PVS1
Leads to in-frame loss or alteration of amino acids within including nucleotides c.1033 and downstream
PVS1_Strong
Proportion of affected transcripts incomplete
Splicing defect leads to out of frame or PTC consequence resulting in NMD
PVS1_Strong
Leads to in-frame loss or alteration of amino acids within including nucleotides upstream and including c.1032
PVS1_Strong
Leads to in-frame loss or alteration of amino acids within including nucleotides c.1033 and downstream
PVS1_Moderate
No variant specific splicing impact observed, or <20% of transcripts altered
N/A, use predictive codes,(PP3,BP7)