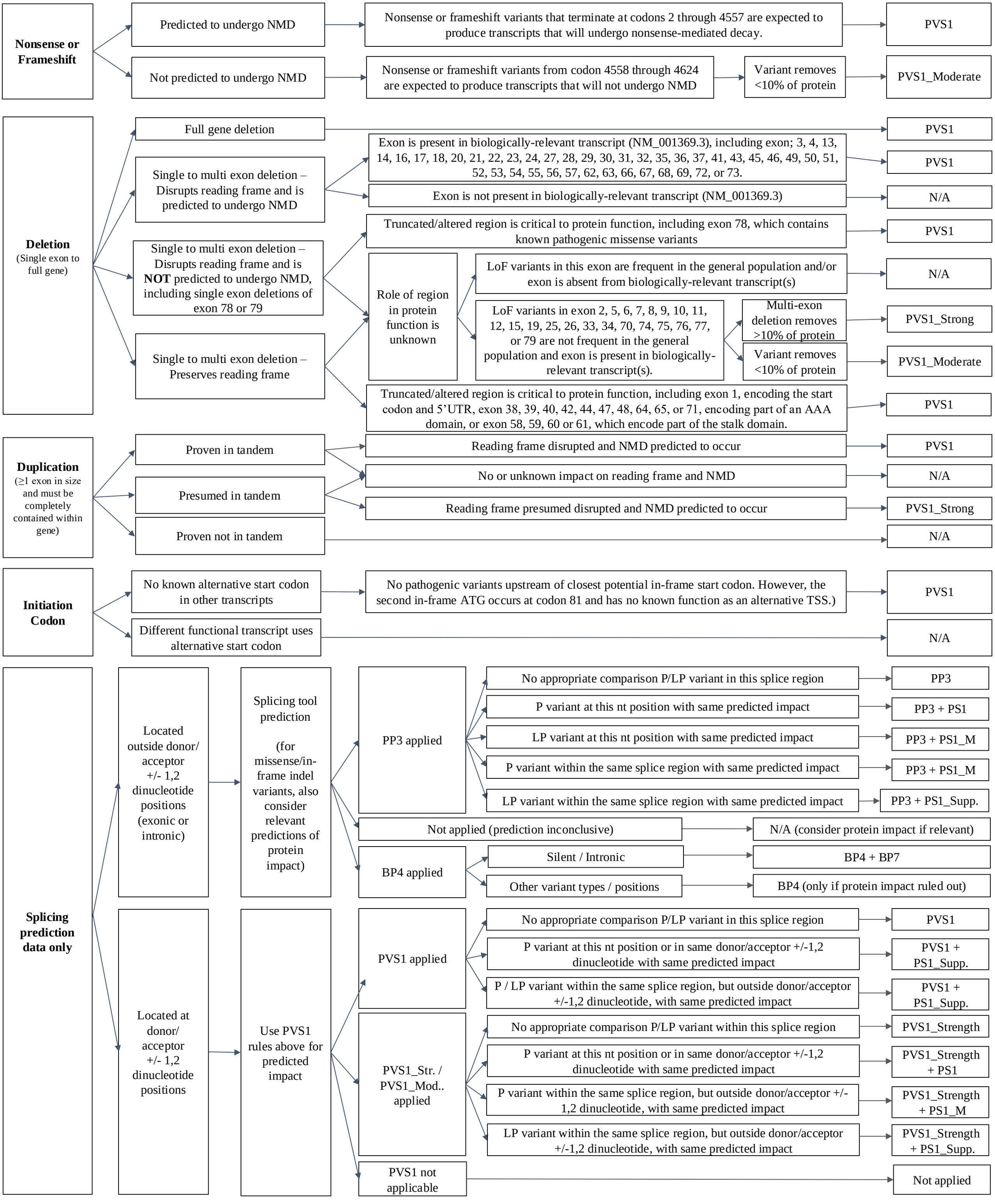
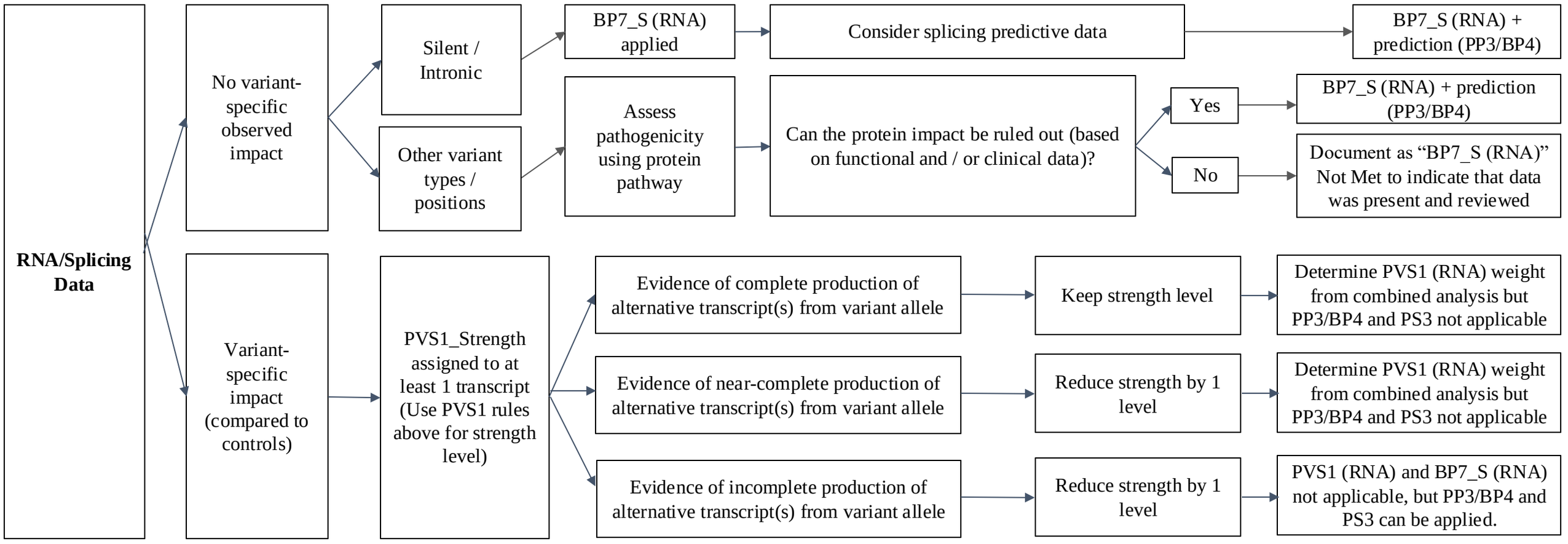

Nonsense or Frameshift
Predicted to undergo NMD
Nonsense or frameshift variants that terminate at codons 2 through 4557 are expected to produce transcripts that will undergo nonsense-mediated decay.
PVS1
Not predicted to undergo NMD
Nonsense or frameshift variants from codon 4558 through 4624 are expected to produce transcripts that will not undergo NMD
Variant removes <10% of protein
PVS1_Moderate
Deletion
(Single exon to full gene)
Full gene deletion
PVS1
Single to multi exon deletion – Disrupts reading frame and is predicted to undergo NMD
Exon is present in biologically-relevant transcript (NM_001369.3), including exon; 3, 4, 13, 14, 16, 17, 18, 20, 21, 22, 23, 24, 27, 28, 29, 30, 31, 32, 35, 36, 37, 41, 43, 45, 46, 49, 50, 51, 52, 53, 54, 55, 56, 57, 62, 63, 66, 67, 68, 69, 72, or 73.
PVS1
Exon is not present in biologically-relevant transcript (NM_001369.3)
N/A
Single to multi exon deletion – Disrupts reading frame and is NOT predicted to undergo NMD, including single exon deletions of exon 78 or 79
Truncated/altered region is critical to protein function, including exon 78, which contains known pathogenic missense variants
PVS1
Role of region in protein function is unknown
LoF variants in this exon are frequent in the general population and/or exon is absent from biologically-relevant transcript(s)
N/A
LoF variants in exon 2, 5, 6, 7, 8, 9, 10, 11, 12, 15, 19, 25, 26, 33, 34, 70, 74, 75, 76, 77, or 79 are not frequent in the general population and exon is present in biologically-relevant transcript(s).
Multi-exon deletion removes >10% of protein
PVS1_Strong
Variant removes <10% of protein
PVS1_Moderate
Single to multi exon deletion – Preserves reading frame
Truncated/altered region is critical to protein function, including exon 1, encoding the start codon and 5'UTR, exon 38, 39, 40, 42, 44, 47, 48, 64, 65, or 71, encoding part of an AAA domain, or exon 58, 59, 60 or 61, which encode part of the stalk domain.
PVS1
Duplication
(≥1 exon in size and must be completely contained within gene)
Proven in tandem
Reading frame disrupted and NMD predicted to occur
PVS1
Presumed in tandem
No or unknown impact on reading frame and NMD
N/A
Reading frame presumed disrupted and NMD predicted to occur
PVS1_Strong
Proven not in tandem
N/A
Initiation Codon
No known alternative start codon in other transcripts
No pathogenic variants upstream of closest potential in-frame start codon. However, the second in-frame ATG occurs at codon 81 and has no known function as an alternative TSS.)
PVS1
Different functional transcript uses alternative start codon
N/A
Splicing prediction data only
Located outside donor/ acceptor +/- 1,2 dinucleotide positions (exonic or intronic)
Splicing tool prediction (for missense/in-frame indel variants, also consider relevant predictions of protein impact)
PP3 applied
No appropriate comparison P/LP variant in this splice region
PP3
P variant at this nt position with same predicted impact
PP3 + PS1
LP variant at this nt position with same predicted impact
PP3 + PS1_M
P variant within the same splice region with same predicted impact
PP3 + PS1_M
LP variant within the same splice region with same predicted impact
PP3 + PS1_Supp.
Not applied (prediction inconclusive)
N/A (consider protein impact if relevant)
BP4 applied
Silent / Intronic
BP4 + BP7
Other variant types / positions
BP4 (only if protein impact ruled out)
Located at donor/ acceptor +/- 1,2 dinucleotide positions
Use PVS1 rules above for predicted impact
PVS1 applied
No appropriate comparison P/LP variant in this splice region
PVS1
P variant at this nt position or in same donor/acceptor +/-1,2 dinucleotide with same predicted impact
PVS1 + PS1_Supp.
P / LP variant within the same splice region, but outside donor/acceptor +/-1,2 dinucleotide, with same predicted impact
PVS1 + PS1_Supp.
PVS1_Str. / PVS1_Mod.. applied
No appropriate comparison P/LP variant within this splice region
PVS1_Strength
P variant at this nt position or in same donor/acceptor +/-1,2 dinucleotide with same predicted impact
PVS1_Strength + PS1
P variant within the same splice region, but outside donor/acceptor +/-1,2 dinucleotide, with same predicted impact
PVS1_Strength + PS1_M
LP variant within the same splice region, but outside donor/acceptor +/-1,2 dinucleotide, with same predicted impact
PVS1_Strength + PS1_Supp.
PVS1 not applicable
Not applied


RNA/Splicing Data
No variant-specific observed impact
Silent / Intronic
BP7_S (RNA) applied
Consider splicing predictive data
BP7_S (RNA) + prediction (PP3/BP4)
Other variant types / positions
Assess pathogenicity using protein pathway
Can the protein impact be ruled out (based on functional and / or clinical data)?
Yes
BP7_S (RNA) + prediction (PP3/BP4)
No
Document as "BP7_S (RNA)" Not Met to indicate that data was present and reviewed
Variant-specific impact (compared to controls)
PVS1_Strength assigned to at least 1 transcript (Use PVS1 rules above for strength level)
Evidence of complete production of alternative transcript(s) from variant allele
Keep strength level
Determine PVS1 (RNA) weight from combined analysis but PP3/BP4 and PS3 not applicable
Evidence of near-complete production of alternative transcript(s) from variant allele
Reduce strength by 1 level
Determine PVS1 (RNA) weight from combined analysis but PP3/BP4 and PS3 not applicable
Evidence of incomplete production of alternative transcript(s) from variant allele
Reduce strength by 1 level
PVS1 (RNA) and BP7_S (RNA) not applicable, but PP3/BP4 and PS3 can be applied.