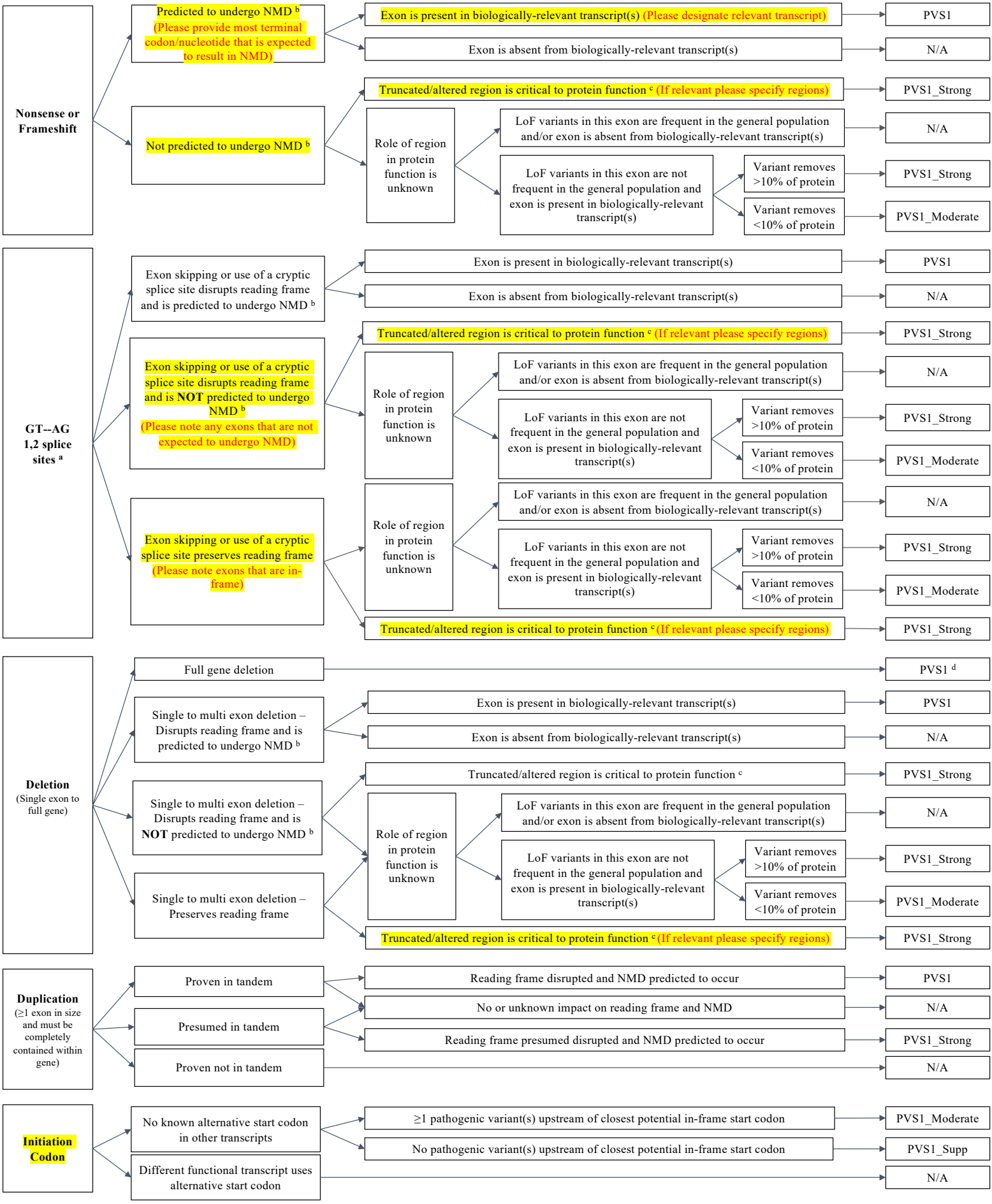
RPGR

Template

Instructions

- VCEPs should modify the PVS1 flowchart for their specifications
- Create a copy of the next slide to modify and attach to your specifications in the CSpec Editor
- Review the boxes highlighted in yellow and modify the text if relevant:
  - Nonsense/Frameshift
    - Predicted to undergo NMD - *Please provide most terminal codon/nucleotide that is expected to result in NMD (if NMD boundary not in penultimate exon please specify).*
      - Exon is present in biologically-relevant transcript(s) - *Please designate relevant transcript*
    - Not predicted to undergo NMD
      - Truncated/altered region is critical to protein function - *If relevant please specify regions*
  - GT--AG 1,2 splice sites (*if AT–AC (U2) splice sites exist please specify)*
    - Exon skipping or use of a cryptic splice site disrupts reading frame and is NOT predicted to undergo NMD - *Please note any exons that are not expected to undergo NMD*
      - Truncated/altered region is critical to protein function - *If relevant please specify regions*
    - Exon skipping or use of a cryptic splice site preserves reading frame - *Please note exons that are in-frame*
      - Truncated/altered region is critical to protein function - *If relevant please specify regions*
  - Deletion (Single exon to full gene)
    - Single to multi exon deletion – Preserves reading frame
      - Truncated/altered region is critical to protein function - *If relevant please specify regions*
  - Initiation Codon - *Please note alt starts if known*


Nonsense or Frameshift
Predicted to undergo NMD [b] (Please provide most terminal codon/nucleotide that is expected to result in NMD)
Exon is present in biologically-relevant transcript(s) (Please designate relevant transcript)
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] (If relevant please specify regions)
PVS1_Strong
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 this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
Variant removes >10% of protein
PVS1_Strong
Variant removes <10% of protein
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 [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] (Please note any exons that are not expected to undergo NMD)
Truncated/altered region is critical to protein function [c] (If relevant please specify regions)
PVS1_Strong
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
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N/A
LoF variants in this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
Variant removes >10% of protein
PVS1_Strong
Variant removes <10% of protein
PVS1_Moderate
Truncated/altered region is critical to protein function [c] (If relevant please specify regions)
PVS1_Strong
Deletion (Single exon to full gene)
Full gene deletion
PVS1 [d]
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]
PVS1_Strong
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)
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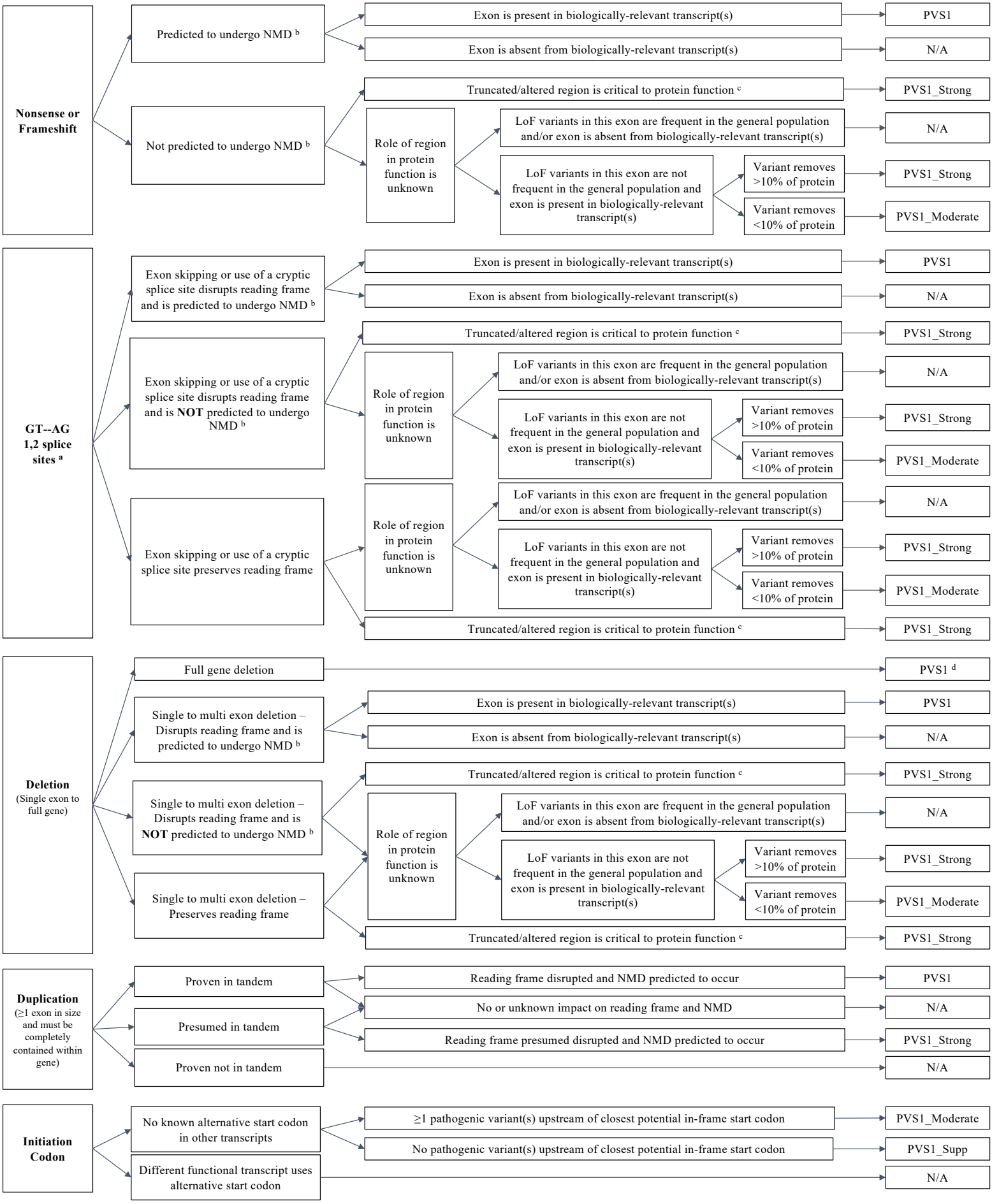
LoF variants in this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
Variant removes >10% of protein
PVS1_Strong
Variant removes <10% of protein
PVS1_Moderate
Single to multi exon deletion – Preserves reading frame
Truncated/altered region is critical to protein function [c] (If relevant please specify regions)
PVS1_Strong
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
≥1 pathogenic variant(s) upstream of closest potential in-frame start codon
PVS1_Moderate
No pathogenic variant(s) upstream of closest potential in-frame start codon
PVS1_Supp
Different functional transcript uses alternative start codon
N/A


Nonsense or Frameshift
Predicted to undergo NMD [b]
Exon is present in biologically-relevant transcript(s)
PVS1
Exon is absent from biologically-relevant transcript(s)
N/A
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PVS1_Strong
Variant removes <10% of protein
PVS1_Moderate
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Role of region in protein function is unknown
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LoF variants in this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
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PVS1_Strong
Variant removes <10% of protein
PVS1_Moderate
Truncated/altered region is critical to protein function [c]
PVS1_Strong
Deletion (Single exon to full gene)
Full gene deletion
PVS1 [d]
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]
PVS1_Strong
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)
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Truncated/altered region is critical to protein function [c]
PVS1_Strong
Duplication (≥1 exon in size and must be completely contained within gene)
Proven in tandem
Reading frame disrupted and NMD predicted to occur
PVS1
No or unknown impact on reading frame and NMD
N/A
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Reading frame presumed disrupted and NMD predicted to occur
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Proven not in tandem
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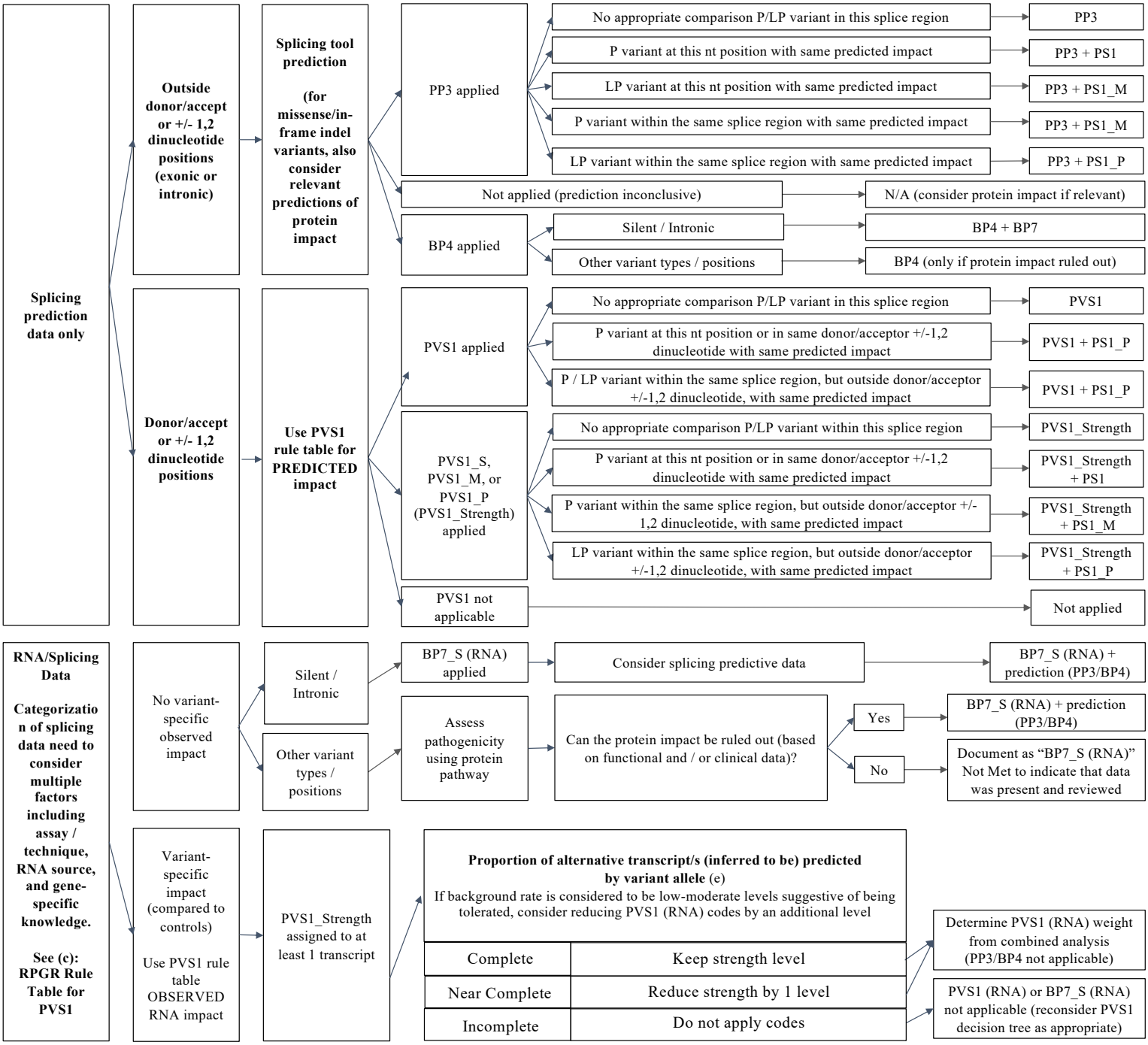
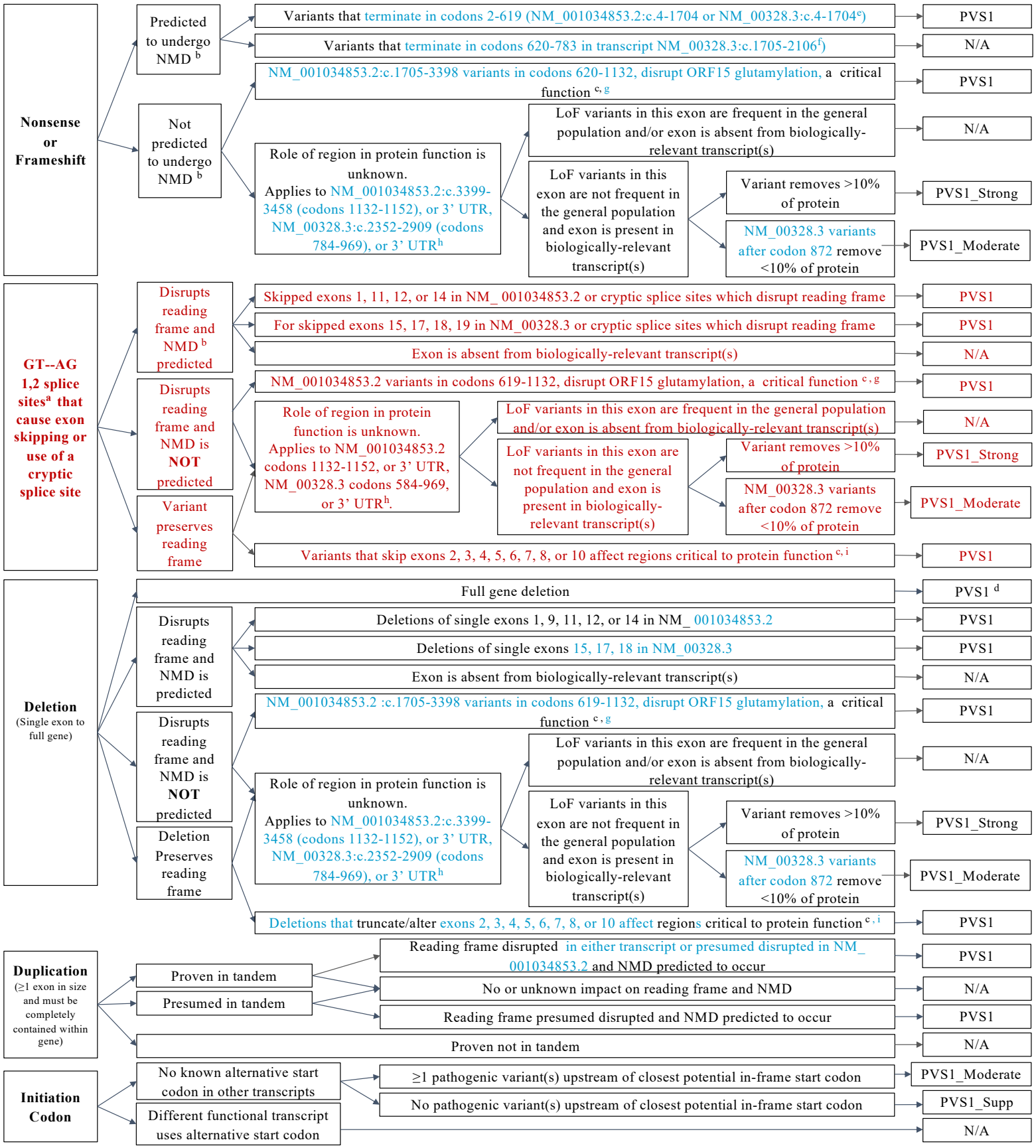
Initiation Codon
No known alternative start codon in other transcripts
≥1 pathogenic variant(s) upstream of closest potential in-frame start codon
PVS1_Moderate
No pathogenic variant(s) upstream of closest potential in-frame start codon
PVS1_Supp
Different functional transcript uses alternative start codon
N/A



PVS1 decision tree for splicing

RPGR


Nonsense or Frameshift
Predicted to undergo NMD [b]
Variants that terminate in codons 2-619 (NM_001034853.2:c.4-1704 or NM_00328.3:c.4-1704[e])
PVS1
Variants that terminate in codons 620-783 in transcript NM_00328.3:c.1705-2106[f])
N/A
Not predicted to undergo NMD [b]
NM_001034853.2:c.1705-3398 variants in codons 620-1132, disrupt ORF15 glutamylation, a critical function [c, g]
PVS1
Role of region in protein function is unknown. Applies to NM_001034853.2:c.3399-3458 (codons 1132-1152), or 3' UTR, NM_00328.3:c.2352-2909 (codons 784-969), or 3' UTR[h]
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 this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
Variant removes >10% of protein
PVS1_Strong
NM_00328.3 variants after codon 872 remove <10% of protein
PVS1_Moderate
GT--AG 1,2 splice sites[a] that cause exon skipping or use of a cryptic splice site
Disrupts reading frame and NMD [b] predicted
Skipped exons 1, 11, 12, or 14 in NM_ 001034853.2 or cryptic splice sites which disrupt reading frame
PVS1
For skipped exons 15, 17, 18, 19 in NM_00328.3 or cryptic splice sites which disrupt reading frame
PVS1
Exon is absent from biologically-relevant transcript(s)
N/A
Disrupts reading frame and NMD is NOT predicted
NM_001034853.2 variants in codons 619-1132, disrupt ORF15 glutamylation, a critical function [c, g]
PVS1
Role of region in protein function is unknown. Applies to NM_001034853.2 codons 1132-1152, or 3' UTR, NM_00328.3 codons 584-969, or 3' UTR[h].
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 this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
Variant removes >10% of protein
PVS1_Strong
NM_00328.3 variants after codon 872 remove <10% of protein
PVS1_Moderate
Variant preserves reading frame
Variants that skip exons 2, 3, 4, 5, 6, 7, 8, or 10 affect regions critical to protein function [c, i]
PVS1
Deletion
(Single exon to full gene)
Full gene deletion
PVS1 [d]
Disrupts reading frame and NMD is predicted
Deletions of single exons 1, 9, 11, 12, or 14 in NM_ 001034853.2
PVS1
Deletions of single exons 15, 17, 18 in NM_00328.3
PVS1
Exon is absent from biologically-relevant transcript(s)
N/A
Disrupts reading frame and NMD is NOT predicted
NM_001034853.2 :c.1705-3398 variants in codons 619-1132, disrupt ORF15 glutamylation, a critical function [c, g]
PVS1
Role of region in protein function is unknown. Applies to NM_001034853.2:c.3399-3458 (codons 1132-1152), or 3' UTR, NM_00328.3:c.2352-2909 (codons 784-969), or 3' UTR[h]
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 this exon are not frequent in the general population and exon is present in biologically-relevant transcript(s)
Variant removes >10% of protein
PVS1_Strong
NM_00328.3 variants after codon 872 remove <10% of protein
PVS1_Moderate
Deletion Preserves reading frame
Deletions that truncate/alter exons 2, 3, 4, 5, 6, 7, 8, or 10 affect regions critical to protein function [c, i]
PVS1
Duplication
(≥1 exon in size and must be completely contained within gene)
Proven in tandem
Presumed in tandem
Reading frame disrupted in either transcript or presumed disrupted in NM_ 001034853.2 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
PVS1_Moderate
No pathogenic variant(s) upstream of closest potential in-frame start codon
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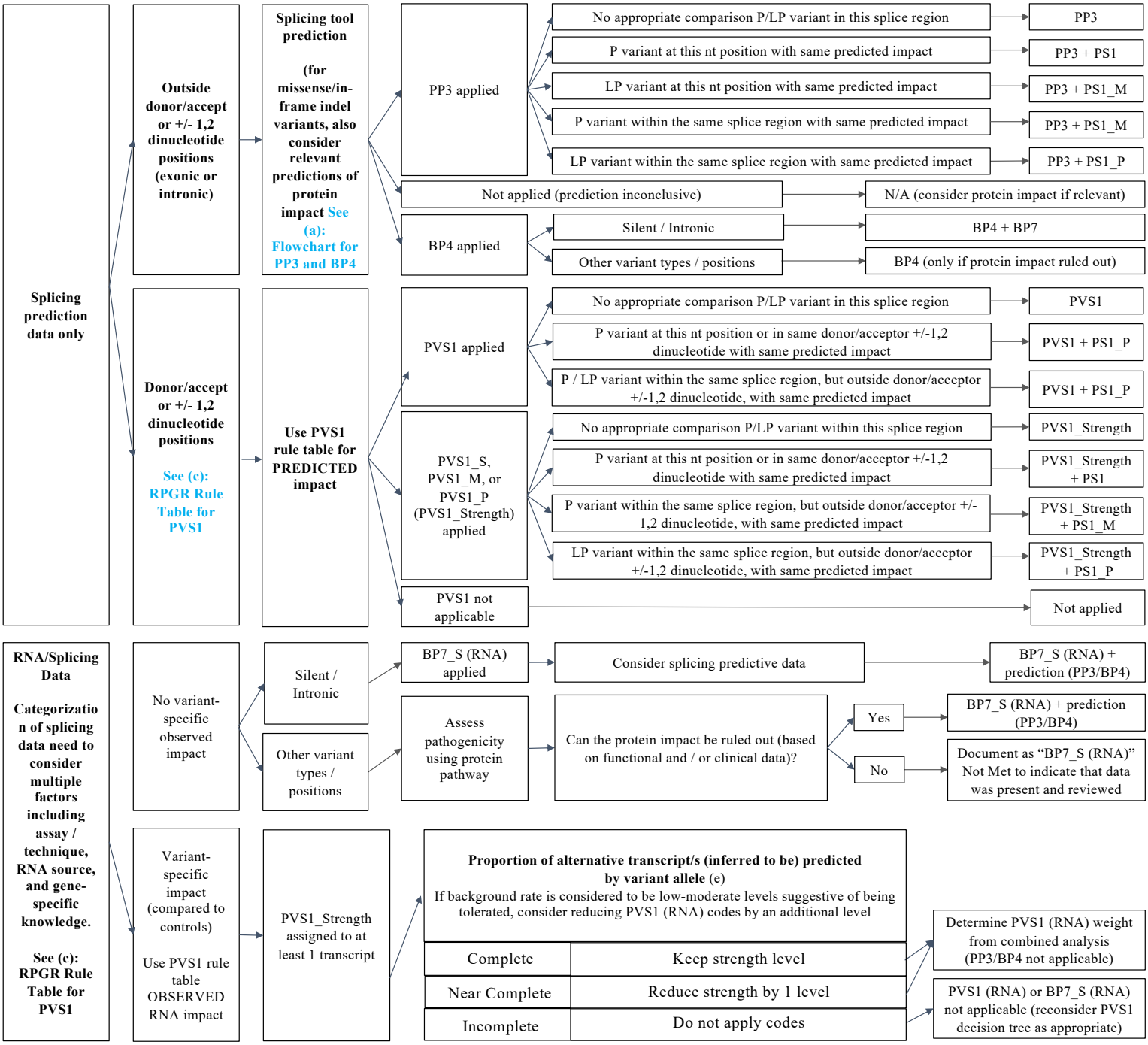
Different functional transcript uses alternative start codon
N/A

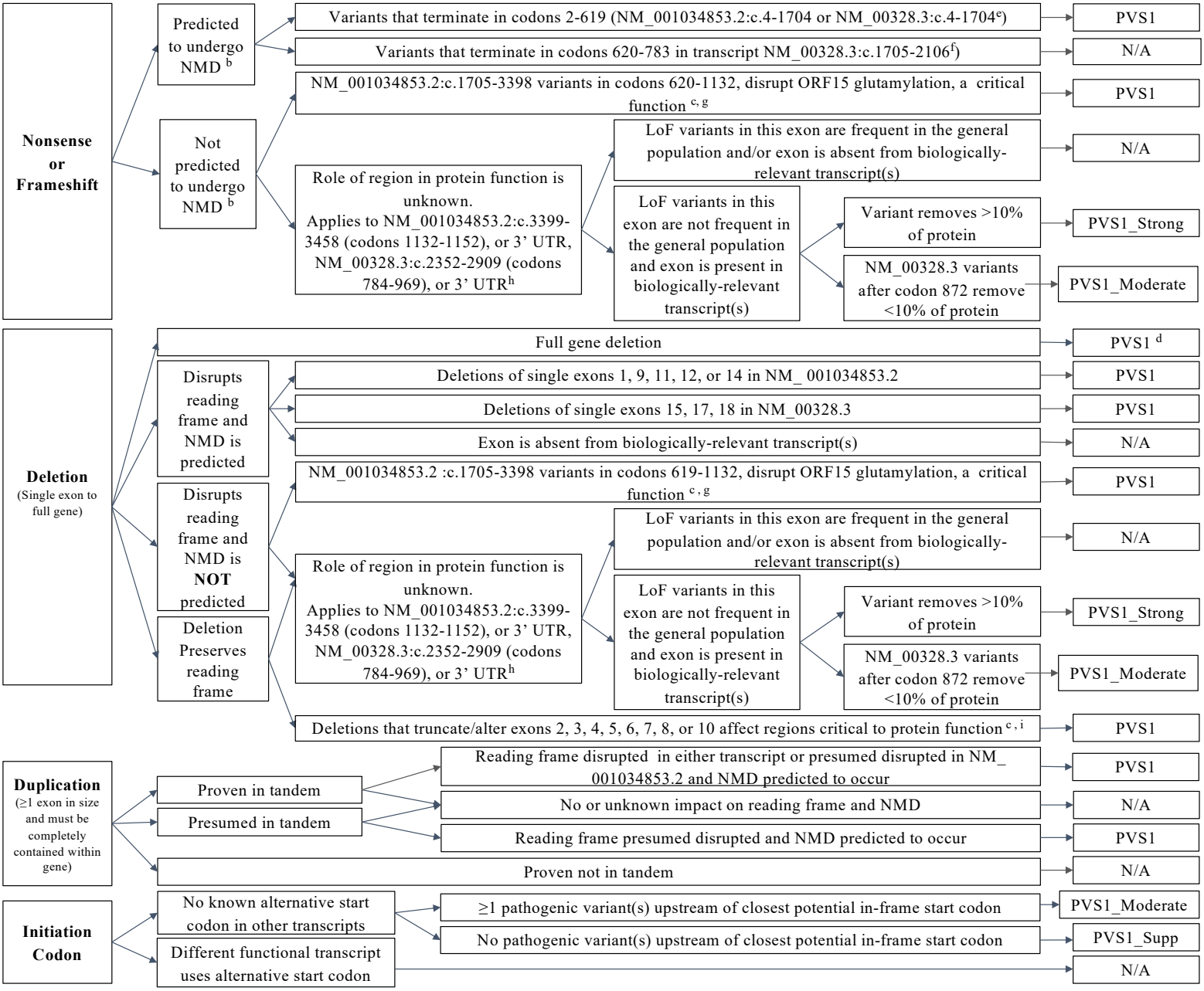


RPGR-specific PVS1 decision tree for splicing

RPGR

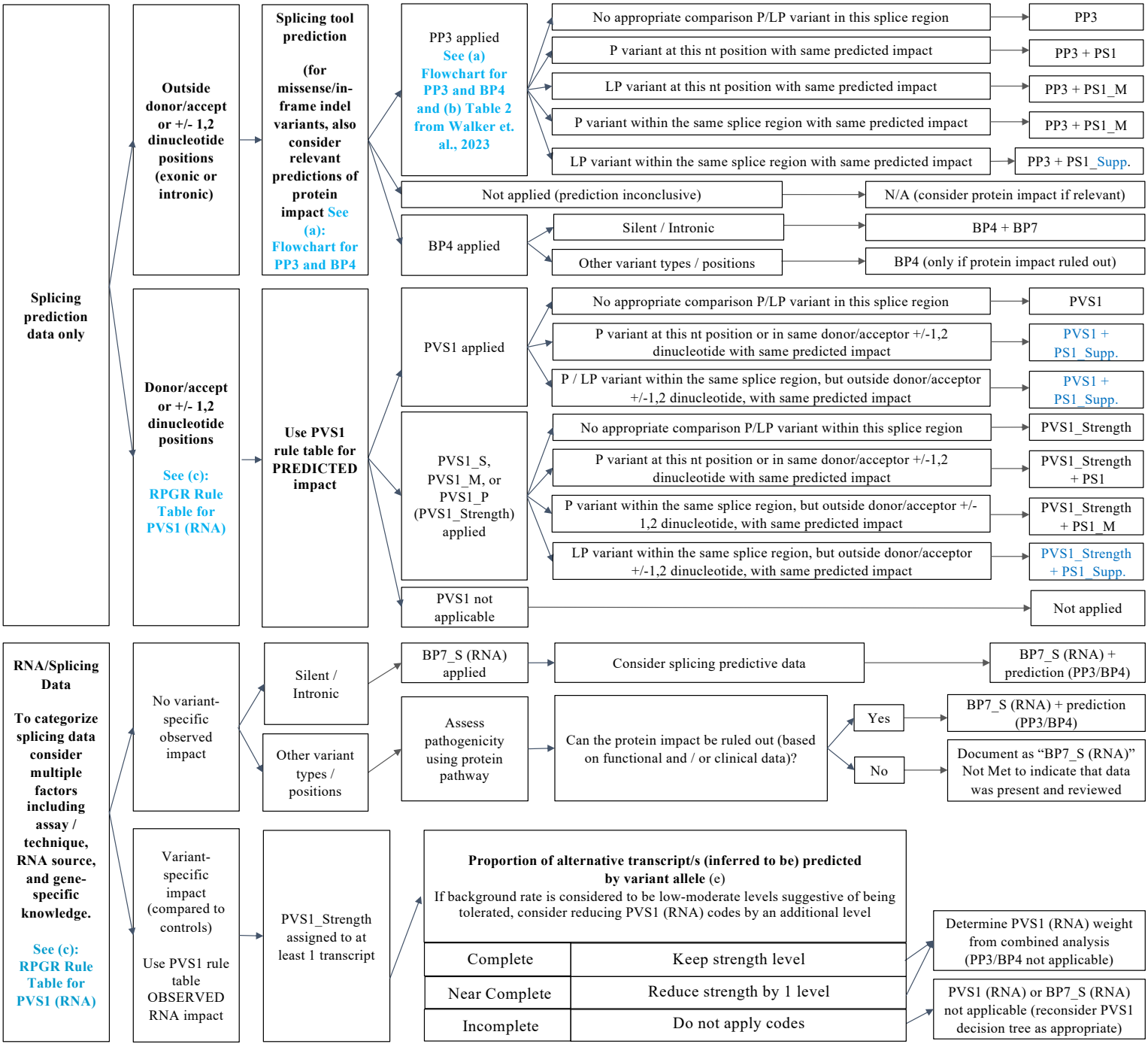
PVS1 Documents 7/30/2024 Version

RPGR PVS1 Decision Tree

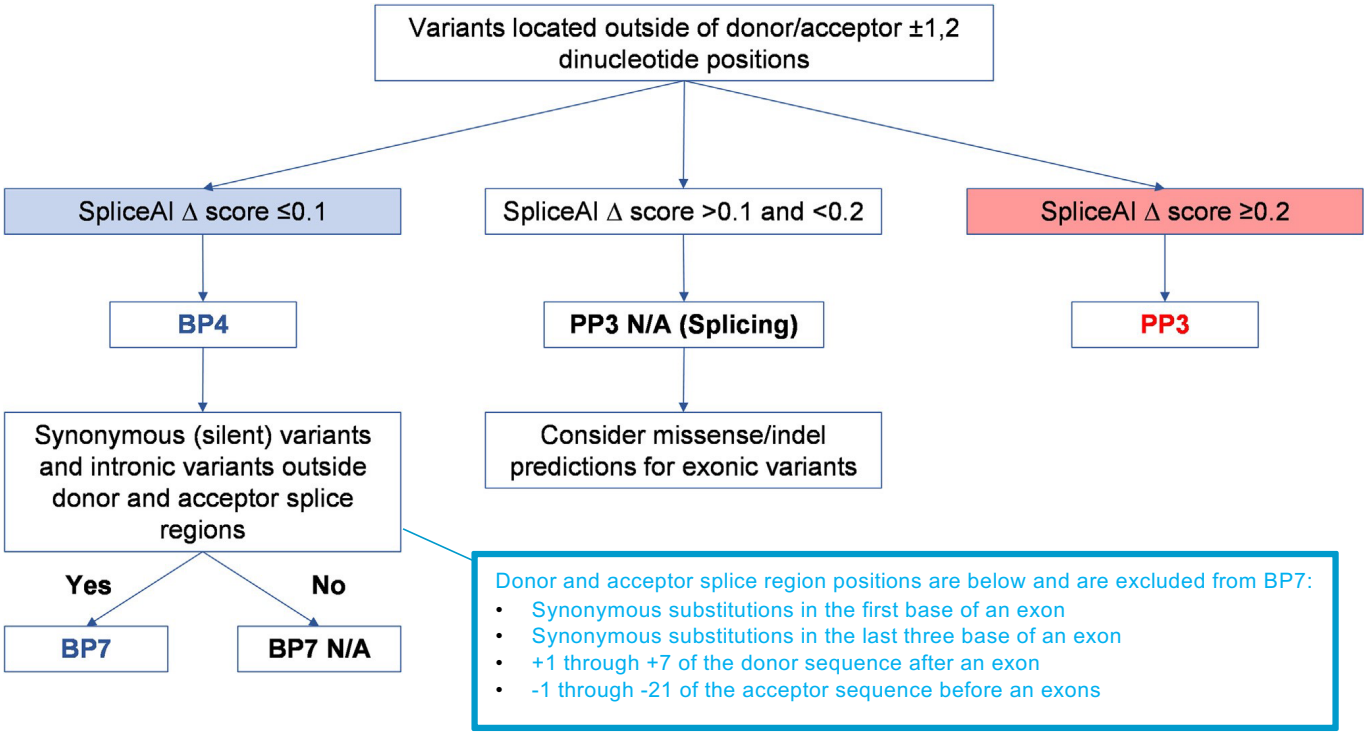


RPGR PVS1 Decision Tree. This is taken from Figure 1 in SVI recommendations for PVS1 interpretation (Tayoun et al., 2018). See also RPGR PVS1 (RNA) Decision Tree. (a) This criterion should not be applied in combination with *in silico* splicing predictions (PP3). Additionally, splice site variants must have no detectable nearby (+/- 20nts) strong consensus splice sequence that may constitute in-frame splicing. (b) NMD prediction based on the premature termination codon not occurring in the 3' most exon or in the 3' most 50bp 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) For a full gene deletion of a known haploinsufficient gene, a pathogenic classification is warranted (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., (2017). For a full gene deletion of RPGR in a male, a pathogenic classification is warranted. NMD, nonsense-mediated decay; LoF, loss of function. Additional notes providing genomic coordinates include (e) Variants that terminate in codons 2-619 in transcripts NM_001034853.2:c.4-1704 and NM_00328.3:c.4-1704 (genomic regions 38,287,910 to 38,327,367) are expected to produce transcripts that will undergo NMD. (f) Variants that terminate in codons 619-783 in transcript NM_00328.3:c.1705-2106 (hg38 genomic regions 38,273,435 to 38,287,910) are expected to produce transcripts that will undergo NMD. (g) Variants in transcript NM_001034853.2:c.1705-3398 (codons 619-1132, hg38 genomic regions 38,287,910 to 38,285,759) are predicted to disrupt the glutamylation in ORF 15 a region that is critical to protein function [c]. (h) Role of region in protein function is unknown. Transcript NM_001034853.2:c.3399-3458 (codons 1132-1152) and 3' UTR. Transcript NM_00328.3:c.2352-2909 (codons 584-969), and 3' UTR. (i) Variants that skip exon 2 which has a defined pathogenic missense variant (PMID37352859) or skip or alter the RCC1 domain in exons 3, 4, 5, 6, 7, 8, 9 or 10 affect regions critical to protein function [c].

RPGR-specific PVS1 (RNA) Decision Tree for Splicing



(a) SpliceAI Flowchart (based on Walker et al., 2023, Figure 4



(b) Table 2 from Walker et al., 2023

Table 2. PS1 code weights for variants with same predicted splicing event as a known (likely) pathogenic variant

Variant under assessment (VUA)	Baseline computational/ predictive code applicable to VUA	Position of comparison variant relative to VUA	PS1 code applicable to VUA	
			with P comparison variant	with LP comparison variant
Located outside splice donor/ acceptor ±1,2 dinucleotide positions	PP3	same nucleotide	PS1	PS1_Moderate
	PP3	within same splice donor/acceptor motif (including at ±1,2 positions)	PS1_Moderate	PS1_Supporting
Located at splice donor/acceptor ±1,2 dinucleotide positions	PVS1	within same splice donor/ acceptor ±1,2 dinucleotide	PS1_Supporting	N/A
	PVS1	within same splice donor/acceptor region, but outside ±1,2 dinucleotide[a]	PS1_Supporting	PS1_Supporting
	PVS1_Strong, PVS1_Moderate, or PVS1_Supporting	within same splice donor/ acceptor ±1,2 dinucleotide	PS1	N/A
	PVS1_Strong, PVS1_Moderate, or PVS1_Supporting	within same splice donor/acceptor motif, but outside ±1,2 dinucleotide[a]	PS1_Moderate	PS1_Supporting

Prerequisite for all: the predicted event of the VUA must precisely match the predicted event of the comparison (likely) pathogenic variant (e.g., both predicted to lead to exon skipping, or both to lead to enhanced use of a cryptic splice motif, AND the strength of the prediction for the VUA must be of similar or higher strength than the strength of the prediction for the comparison [likely] pathogenic variant). For an exonic variant, predicted or proven functional effect of missense substitution(s) encoded by the VUA and (likely) pathogenic variant should also be considered before application of this code. Dinucleotide positions refer to donor and acceptor dinucleotides in reference transcript(s) used for curation. Designated donor and acceptor motif ranges should be based on position weight matrices for intron category (see methods). For GT-AG introns these are defined as follows: the donor motif, last 3 bases of the exon and 6 nucleotides of intronic sequence adjacent to the exon; acceptor motif, first base of the exon and 20 nucleotides upstream from the exon boundary. Consider other motif ranges for non-GT-AG introns.

[a]If relevant, splicing assay data for a pathogenic variant outside a ±1,2 dinucleotide position may be used to update a PVS1 decision tree and hence the applicable PVS1 code for a ±1,2 dinucleotide variant.

(c) RPGR PVS1 (RNA) rule table (for +- 1,2 changes and RNA splicing assays) for in the retinal-specific transcript NM_001034853.2 and broadly expressed transcript NM_00328.3 coordinates are shown, black exons are common to both red is the retinal-specific ORF15 exon and preceding exon 14, blue are splice sites in NM_00328.3 only.

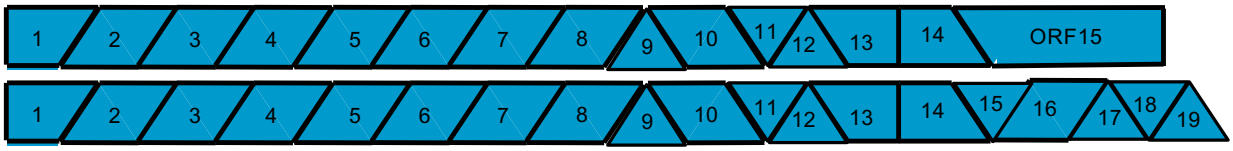
Based on generic gene schematic (shown below) proposed by Walker et al., 2023 with the following modifications:

1. Pathogenic missense variants have been identified in exons 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and ORF15 which are considered to be "critical to protein function", requirement for being more that 10% of total protein length does not apply.
2. ATG initiation site is located in exon 1 so 5' UTR recommendation (A) does not apply.
3. No potential "rescue isoforms" are known.
4. Use this table to assign appropriate PVS1 code and rationale:

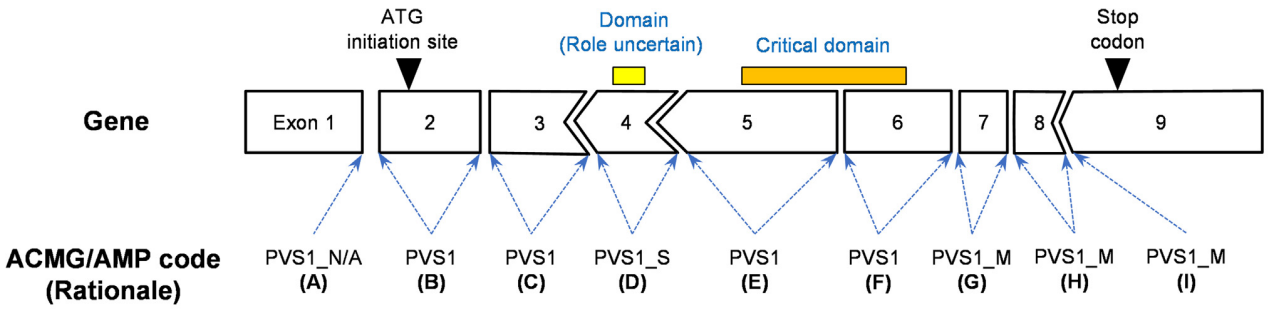
	NM_000328.3	Transcript Start		Transcript End		HG38 coordinates (reverse strand)		Exon skipping leads to preserved reading frame or frameshift (FS) with nonsense mediated decay (NMD)?		PFs1 code for +/- 1,2 dinucleotide change and rationale from Walker et al. below	Exon known to be critical to protein function
	NM_001034853.2	3' acceptor position		5' donor position		Genome Start	Genome End	FS	NMD		
	Exon 1	1	c.-142	170	c.28	38,327,509	38,327,340	FS	NMD	PVS1 (B)	Yes
	Exon 2	171	c.29	296	c.154	38,323,524	38,323,399	in frame	No NMD	PVS1 (G)	No
	Exon 3	297	c.155	389	c.247	38,322,945	38,322,853	in frame	No NMD	PVS1 (F)	Yes
	Exon 4	390	c.248	452	c.310	38,321,089	38,321,027	in frame	No NMD	PVS1 (F)	Yes
	Exon 5	453	c.311	611	c.469	38,318,987	38,318,829	in frame	No NMD	PVS1 (F)	Yes
	Exon 6	612	c.470	761	c.619	38,317,465	38,317,316	in frame	No NMD	PVS1 (F)	Yes
	Exon 7	762	c.620	920	c.778	38,310,773	38,310,615	in frame	No NMD	PVS1 (F)	Yes
	Exon 8	921	c.779	1076	c.934	38,304,790	38,304,635	in frame	No NMD	PVS1 (F)	Yes
	Exon 9	1077	c.935	1201	c.1059	38,301,371	38,301,247	FS	NMD	PVS1 (C)	Yes
	Exon 10	1202	c.1060	1387	c.1245	38,299,141	38,298,956	in frame	No NMD	PVS1 (F)	Yes
	Exon 11	1388	c.1246	1556	c.1414	38,297,452	38,297,284	FS	NMD	PVS1 (C)	Yes
	Exon 12	1557	c.1415	1648	c.1506	38,291,484	38,291,393	FS	NMD	PVS1 (C)	Yes
	Exon 13	1649	c.1507	1714	c.1572	38,291,024	38,290,959	in frame	No NMD	PVS1 (G)	Yes
NM_001034853.2	Exon 14	1715	c.1573	1895	c.1753	38,288,041	38,287,861	FS	No NMD	PVS1 (J)	No
NM_000328.3	Exon 14	1715		1895		38,288,041	38,287,861	FS	NMD	PVS1 (C)	No
NM_001034853.2	Exon ORF15	1896	c.1754	4733	c.*3459	38,287,245	38,284,408	in frame	No NMD	PVS1 (F)	Yes
NM_000328.3	Exon 15	1896	c.1754	2047	c.1905	38,287,245	38,287,094	FS	NMD	PVS1 (C)	Yes
NM_000328.3	Exon 16	2048	c.1906	2233	c.2091	38,276,772	38,276,587	in frame	No NMD	PVS1 (G)	No
NM_000328.3	Exon 17	2234	c.2092	2291	c.2149	38,275,146	38,275,089	FS	NMD	PVS1 (D)	No
NM_000328.3	Exon 18	2292	c.2150	2389	c.2241	38,273,477	38,273,386	FS	No NMD	PVS1 (H)	No
NM_000328.3	Exon 19	2384	c.2242	3053	c.*463	38,269,832	38,269,163	FS	No NMD	PVS1 (I)	No

Start codon	143	c.1	145	c.3	38,327,368	
Nearest in-frame start codon	164	c.21	166	c.23	38,327,346	This alternate start codon precludes use of PVS1(B)
Next nearest in-frame start codon	172	c.30	174	c.32	38,327,338	This alternate start codon is in exon 3.
Stop codon ORF15	3599	c.*3457	3601	c.*3459	38,285,542	
Stop codon exon 19	2446	c.*2304	2448	c.*2306	38,269,627	
NDM predicted cutoff NM001034853.2	1845	c.1702	1847	c.1704	38,287,897	
NMD predicted cutoff NM_000328.3	2349	c.2106	2351	c.2108	38,273,420	
Stop codon after stop-loss in ORF15	3710	c.3567	3712	c.3569	38,285,431	+37 codons
Stop codon after stop-loss in exon 19	2639	c.2496	2641	c.2498	38,269,577	+17 codons

(d) RPGR exon map: The retinal-specific transcript NM_001034853.2 is on the top and NM_00328.3 is on the bottom. Splice sites for exons 1-14 and the start of exon 15 or ORF15 are the same in both transcripts. The overhang shown at the top is a two-nt overhang, overhang on bottom is a one-nt overhang. Parallel lines represent in-frame junctions (e.g. deletion of exons 2+3 is in frame, deletion of 8+9 is out of frame.



(e) Generic PVS1 schematic – Figure 2 from Walker et al., 2023



(A) 5' UTR region - No splicing alteration predicted or use of a cryptic splice motif does not affect the coding sequence.
(B) Exon skipping or use of a cryptic splice motif eliminates the initiation codon and there are no alternative start codons.
(C) Exon skipping or use of a cryptic splice motif disrupts reading frame and is predicted to undergo NMD
(D) Exon skipping or use of a cryptic splice motif preserves reading frame, and removes a region (>10% of the protein) which has not been established as critical to protein function.
(E) Exon skipping or use of a cryptic splice motif disrupts reading frame and is predicted to undergo NMD
(F) Exon skipping or use of a cryptic splice motif preserves reading frame, and removes a region which has been established as critical to protein function
(G) Exon skipping or use of a cryptic splice motif preserves reading frame, and removes a region (<10% of the protein) which has not been established as critical to protein function.
(H) Exon skipping or use of a cryptic splice motif disrupts reading frame and is not predicted to undergo NMD, and removes a region (<10% of the protein) which has not been established as critical to protein function.
(I) Exon skipping or use of a cryptic splice motif disrupts reading frame and is not predicted to undergo NMD, and removes a region (<10% of the protein) which has not been established as critical to protein function.

Figure 2. Schematic demonstrating assignment of gene-specific codes to splice donor/acceptor ±1,2 dinucleotide variants based on a modified version of the original ClinGen SVI PVS1 framework
Original framework refers to recommendations as published.[2] It is important to note that each PVS1 assigned weight may be reduced if there is evidence of potential rescue mechanisms. For example, skipping of either exon 4 or 7 may lead to a protein that retains partial function. Annotating gene-specific lists of naturally occurring splicing events can provide greater evidence of potential "rescue" isoforms. Also see Box S1.

XLIRD VCEP proposes to add:
(J, edit of H) Exon skipping or use of a cryptic splice motif disrupts reading frame and is not predicted to undergo NMD, and removes a region (<10% of the protein) which has not been established as critical to protein function, but it disrupts a region in the next exon which has been established as critical to protein function. PVS1