P593 - Piloting the Forthcoming ACMG/AMP/CAP/ClinGen Standards for Sequence Variant Classification

To be notified of the Phase 3 Pilot, join our SVCv4 User Group

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Introduction & Methods

ACMG, AMP, CAP, and ClinGen are working on updated standards for sequence variant classification (SVC), referred to as **SVC v4.0**.

SVC v4.0 uses a Bayesian, points-based system and flow diagrams that guide curators through evidence application.

To evaluate the validity and usability of the draft standards, we launched a pilot involving clinical laboratories with expertise in variant classification.

- **30 variants (Table 1)** of varying impact and evidence were selected to test specific components of the v4 framework
- Supporting evidence, including mechanism of disease, prevalence and penetrance estimates, and clinical data were provided to avoid variation due to access to evidence
- All curations were performed in a pilot curation interface developed by ClinGen
- On average each variant had 26 classifications (range 23-30)
- Concordance was assessed on three distinct scales:
  - 3-level (P/LP, VUS, LB/B), 5-level (P, LP, VUS, LB, B), and a 7-level scale with VUS subclassified into VUS-high, VUS-mid, and VUS-low

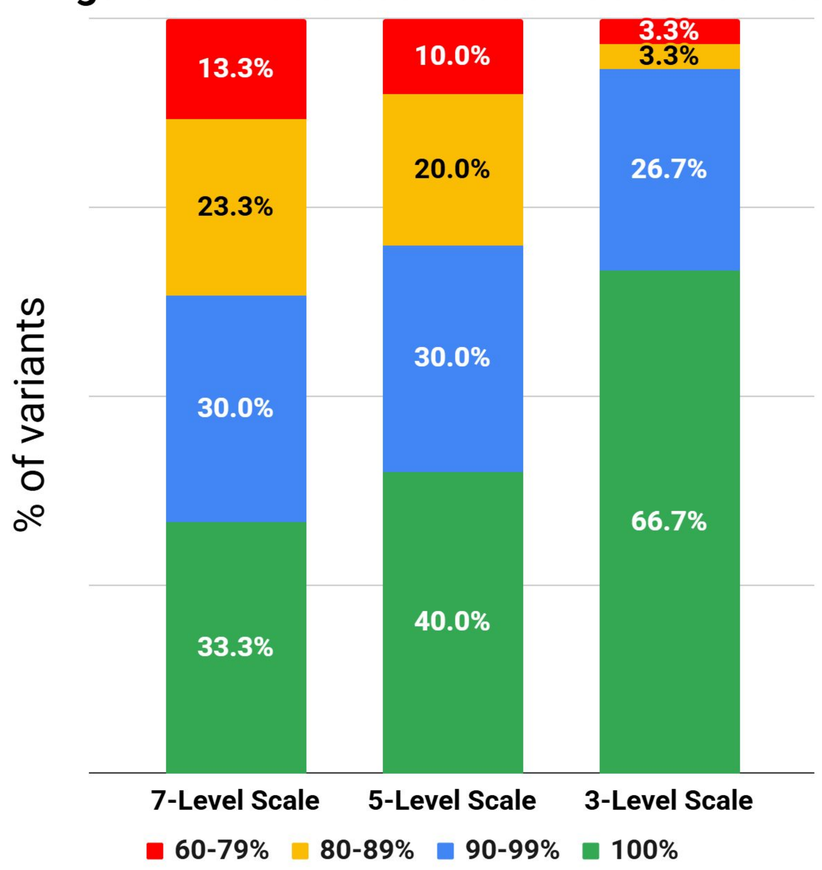
Table 1: Comparison of 30 Pilot Variant Classifications

Variant Type	Variant Evidence	Expected Class (Pts)	Classifications							% Disagree	Classification Concordance		
			P	LP	VUS			LB	B		7-level	5-level	3-level
					H	M	L						
Canonical Splice Site	Inframe impact	P (+11)	22	5	-	1	-	-	-	0.0%	*78.6%*	78.6%	96.4%
	Inframe impact	VUS-L (+1)	-	-	1	4	20	-	-	16.0%	80.0%	100.0%	100.0%
	Splicing data	LP (+7)	-	25	-	-	-	-	-	8.0%	100.0%	100.0%	100.0%
Frameshift	LOF not mech	VUS-L (+0.5)	-	-	-	-	30	-	-	0.0%	100.0%	100.0%	100.0%
	Last exon	LP (+8)	2	26	1	1	-	-	-	0.0%	86.7%	86.7%	93.3%
	Strong pheno	P (+15)	29	-	-	-	-	-	-	3.4%	100.0%	100.0%	100.0%
	LOF mechanism?	VUS-H (+4)	-	-	18	5	-	-	-	0.0%	*78.3%*	100.0%	100.0%
Nonsense	Exon relevance	VUS-L (0)	-	-	-	-	25	1	3	3.4%	86.2%	86.2%	86.2%
Met1	Alt Met	VUS-L (0)	-	-	-	-	24	-	-	12.5%	100.0%	100.0%	100.0%
Deletion	Inframe impact	LP (+8)	7	16	2	-	-	-	-	24.0%	*64.0%*	64.0%	92.0%
	Inframe impact	LP (+7)	-	16	9	1	-	-	-	11.5%	*61.5%*	61.5%	61.5%
	OOF impact	P (+11)	23	4	-	-	-	-	-	3.7%	85.2%	85.2%	100.0%
	Repeat region	B (-7)	-	-	-	-	-	1	28	0.0%	96.6%	96.6%	100.0%
Intronic	Splicing data	LB (-3)	-	-	-	-	1	22	4	11.1%	81.5%	81.5%	96.3%
Missense	Alt cause	B (-4)	-	-	-	-	-	-	25	4.0%	100.0%	100.0%	100.0%
	Alt cause	LB (-1)	-	-	-	-	-	25	2	7.4%	92.6%	92.6%	100.0%
	Conflicting data	VUS-L (+0)	-	-	-	-	25	1	-	15.4%	96.2%	96.2%	96.2%
	Limited pheno	VUS-H (+5)	-	2	27	-	-	-	-	3.4%	93.1%	93.1%	93.1%
	Pop data only	LB (-3)	-	-	-	-	-	27	1	3.6%	96.4%	96.4%	100.0%
	Pop data only	LB (-1)	-	-	-	-	2	24	-	42.3%	92.3%	92.3%	92.3%
	Pop data only	LB (-1)	-	-	-	-	1	25	-	23.1%	96.2%	96.2%	96.2%
	Predict data only	LP (+8)	-	25	-	-	-	-	-	8.0%	100.0%	100.0%	100.0%
	Predict data only	LB (-1)	-	-	-	-	-	26	-	42.3%	100.0%	100.0%	100.0%
	Fxnl data	P (+11)	26	-	-	-	-	-	-	3.8%	100.0%	100.0%	100.0%
	Fxnl data	LP (+8)	-	25	-	-	-	-	-	4.0%	100.0%	100.0%	100.0%
	Fxnl data	B (-5)	-	-	-	-	-	3	23	19.2%	88.5%	88.5%	100.0%
	Strong pheno	P (+16)	28	-	-	-	-	-	-	0.0%	100.0%	100.0%	100.0%
	Splicing data	P (+15)	27	1	-	-	-	-	-	3.6%	96.4%	96.4%	100.0%
Synonymous	Splicing data	P (+12)	22	5	-	-	-	-	-	7.4%	81.5%	81.5%	100.0%
	Unaffected	LB (-2)	-	-	-	-	-	23	1	0.0%	95.8%	95.8%	100.0%

Results & Discussion

- Of the 30 variants selected to test various workflows and scenarios, **93.3% (28/30) reached >90%** concordance on the 3-level classification scale (**Figure 1**), with only one <80%
- At the 7-level scale, **4 variants had <80% concordance** (**yellow**)
  - 3/4 are large inframe deletions suggesting further guidance on how to determine the impact of inframe events is needed
- Curators were asked if they agreed with the classification reached based on the evidence provided (**%Disagree; Table 1**)
  - For 6 variants (20%) curators all agreed with the classification and for 14 variants (46.7%) only one or two curators indicated disagreement with the classification
  - **4 variants had >20% disagreement** (**blue; Table 1**)
    - 3/4 are variants that reach LB based on only -1 point
- Through SVC v4.0 pilots we are ensuring that the framework is valid and instructions for use are clear before finalization
- These results and additional feedback obtained have identified components of SVC v4.0 that needed further updates or guidance on use and we have been making changes to address these points
- Phase 3 Pilot, open to all, anticipated to start March 2026

Figure 1: Pilot Classification Concordance



Participating Sites: Ambry, ARUP, Baylor Genetics, Broad Institute, Cedars Sinai, CHEO, GeneDx, Illumina, Institute of Cancer Research, LabCorp, MGB LMM, Mayo Clinic, Myriad, Natera, Nationwide Children's, NY Genome Center, NIAID, NHGRI, Quest Diagnostics, Rady Children's, Royal Melbourne Hospital, Sheffield Children's, Stanford, Hospital for Sick Children, UCLA, UNC Chapel Hill, Vanderbilt, Yale

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