**BENCHMARKING AN AUTOMATED VARIANT CLASSIFICATION ENGINE (AVCE) ALGORITHM USING CLINVAR: RESULTS OF A TIME-CAPSULE EXPERIMENT**

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ntroduction: DNA sequencing technology has evolved rapidly with the advent of high-throughput next-generation sequencing (NGS). To address challenges in NGS interpretation, a novel algorithm, which integrates human DNA sequences with phenotyping, has been developed, based on the American College of Medical Genetics and Genomics (ACMG) standards and guidelines. To validate this novel automated Variant Classification Engine (aVCE), we performed a blinded time-capsule experiment to predict algorithm ability to classify variants after the time capsule cutoff date. Methods: ClinVar is a publicly available archive of reports that details relationships among variations and phenotypes, with supporting evidence. The aVCE was 'trained' on ClinVar database (version 30-06-17). Variants with Reference/Submission ClinVar (RCV/SCV) creation dates before and after 01-07-16 were marked as 'Train' and 'Test,' respectively. Variants with ≥2 ClinVar stars were included in the 'Test' set. Using ACMG guidelines, the aVCE was applied to the 'Test' set to classify variants as pathogenic (P), likely pathogenic (LP), uncertain significance (VUS), likely benign (LB), and benign (B). In accordance with the ACMG guidelines, additional tiers for sub-classification of VUS were used: 'uncertain significance, leaning benign (VUS-LB), weak leaning pathogenic (VUS-WLP), and strong leaning pathogenic (VUS-SLP). Results also were characterized from a clinical perspective, i.e., clinically 'actionable' (P/LP) versus 'non-actionable' (VUS/LB/B) variants and benchmarked against the ClinVar classifications to determine sensitivity and specificity.Results: When compared against ClinVar submissions from clinical laboratories and high-certainty entries, the proprietary aVCE classified clinically 'actionable' (P/LP) and 'non-actionable' (VUS/LB/B) variants with very high sensitivity (99.29%, 1262/1271) and specificity (100%).Conclusions: The aVCE algorithm, predicts with very high sensitivity and specificity whether a variant in the future would be categorized as clinically 'actionable' versus 'non-actionable.' Algorithms that apply the latest computational methodologies to ACMG guidelines may assist variant scientists with classification and interpretation of variants, including those with limited clinical information.

**Abstract image**

*Table.* Benchmarking an automated Variant Classification Engine (aVCE) using a time capsule of the ClinVar database

| *aVCE* / ClinVar | *B* | *LB* | *US-LB* | *VUS* | *US-WLP* | *US-SLP* | *LP* | *P* |
|---|---|---|---|---|---|---|---|---|
| B | 164 | 9 | 69 | 98 | 0 | 0 | 0 | 0 |
| LB | 1 | 1 | 55 | 16 | 2 | 3 | 0 | 0 |
| LP | 0 | 0 | 1 | 0 | 0 | 2 | 4 | 5 |
| P | 0 | 0 | 0 | 0 | 2 | 4 | 1250 | 3 |

| *aVCE* / ClinVar | *'Actionable'* | *'Non-actionable'* | Sensitivity | Specificity |
|---|---|---|---|---|
| 'Actionable' | 1262 | 9 | 0.9929 | 1 |
| 'Non-actionable' | 0 | 418 | | |