An Artificial Intelligence Engine for High-Throughput Matching of Genetic Variants to their ACMG/AMP Classification for Inherited Disease Gene Panels

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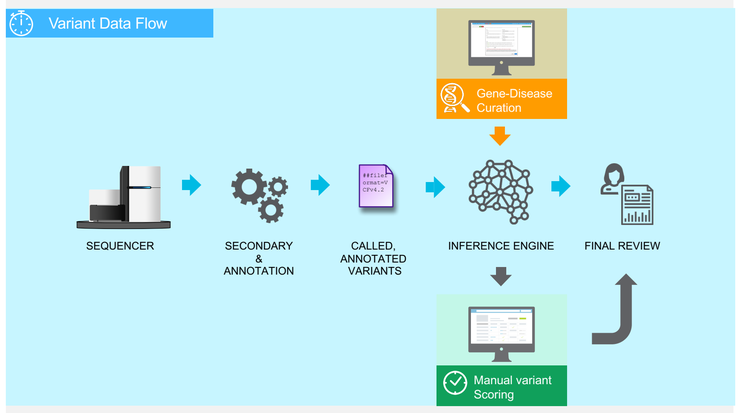
INTRODUCTION

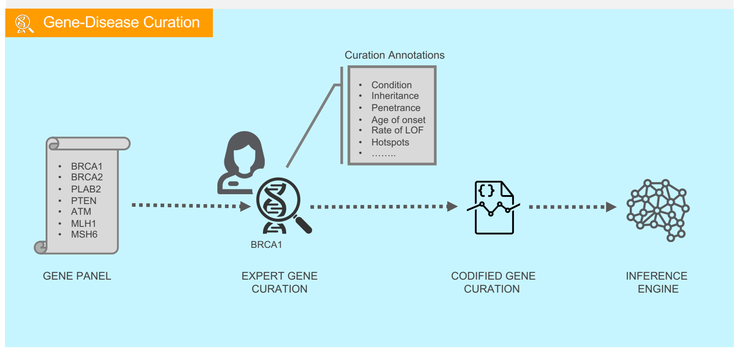
The ACMG/AMP evidence-based guidelines for variant pathogenicity assessment define 28 criteria to evaluate different types of supporting evidence. Criteria are combined to classify a variant as either pathogenic (P), likely-pathogenic (LP), benign (B), likely-benign (LB), or uncertain significance (VUS). Although widely adopted for clinical interpretation of variants this process has remained predominantly manual and time-consuming. The rich evidence needed to classify variants is difficult to effectively incorporate in manual classification resulting in discrepancies of interpretation, excessive specialized reviewing labor, and high costs. Current informatics tools aimed to ease the application of the guidelines do not completely automate the process. For these reasons we developed **Fabric ACE**, an **A**rtificial Intelligence **C**lassification **E**ngine to automatically infer the classification of genetic variants in gene panel testing. ACE utilizes a forward-chaining inference engine at its core to implement the ACMG–AMP criteria and returns predicted classifications for most input variants in previously curated panels, including the criteria completed and necessary for classification.

Methods

We developed an artificial intelligence variant classification engine utilizing forward-chaining inference, which automatically evaluates the ACMG–AMP criteria. ACE returns a predicted classification for each variant, or flags variants with inconclusive classifications for further manual review. Our engine incorporates rule assessments for specific combinations of gene disease conditions as proposed by expert panels. Separating the rule specification from the code that executes the inference allows for refinement and customization of the criteria without modification of the validated inference engine code.



A critical input to the engine is careful expert curation of the gene-disease relationship attributes such as inheritance, penetrance, onset, etc., and computed features such as hotspots, protein motifs, constraint, etc. Other relevant features are computed automatically for each variant using our comprehensive variant annotation pipeline. Those features include transcript, variant impact, state-of-the-art variant deleteriousness scores such as Revel (Ioannidis et al. AJHG 99:877–885, 2016), ClinPred (Alirezaie, et al., AJHG 103:474-483, 2018), and VVP (Flygare et al. BMC Bioinformatics 19:57, 2018), NMD and cryptic splice site predictors, and others.



Curated Panels

We curated genes for a number of commonly used panels as our initial implementation for benchmarking as shown below.

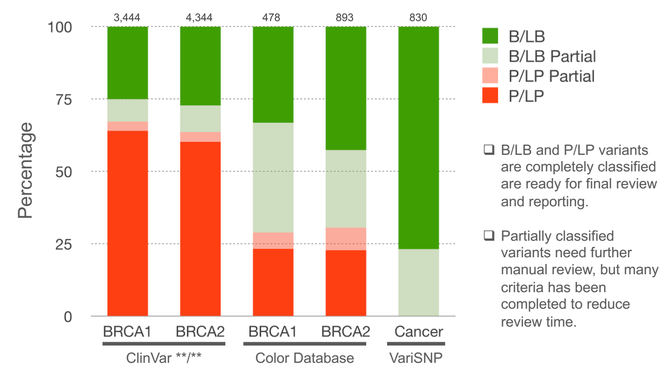
INHERITED CANCER RISK	Includes 15 genes with high evidence of association with cancer risk						
ATM	BRCA2	CDH1	MSH2	NBN	PMS2	RAD51C	TP53
BRCA1	BRIP1	MLH1	MSH6	PALB2	PTEN	STK11	

ACMG SECONDARY FINDINGS	Incudes 59 genes that the ACMG recommends pathogenic variants should be reported due to high medical relevance								
BRCA1	PTEN	RB1	CACNA1S	KCNQ1	MYH11	PCSK9	SCN5A	SMAD4	TPM1
BRCA2	STK11	ACTA2	DSC2	LDLR	MYH7	PKP2	SDHAF2	TGFBR1	TSC1
MLH1	TP53	ACTC1	DSG2	LMNA	MYL2	PRKAG2	SDHB	TGFBR2	TSC2
MSH2	ATP7B	APC	DSP	MEN1	MYL3	RET	SDHC	TMEM43	VHL
MSH6	COL3A1	APOB	FBN1	MUTYH	NF2	RYR1	SDHD	TNNI3	WT1
PMS2	GLA	BMPR1A	KCNH1	MYBPC3	OTC	RYR2	SMAD3	TNNT2	

NEWBORN SCREEINING	Includes 30 genes for supplementary screening for serious health conditions at birth								
COL3A1	ALDOB	ARSB	CTNS	DMD	GALC	GJB2	IDUA	NAGLU	SMN1
GLA	ALPL	ASAH1	CYP27A1	G6PD	GAMT	GUSB	LIPA	SGSH	SMPD1
RB1	ARSA	ATP7A	DHCR7	GAA	GBA	IDS	MAN2B1	SLC7A7	TPP1

Benchmarking Results

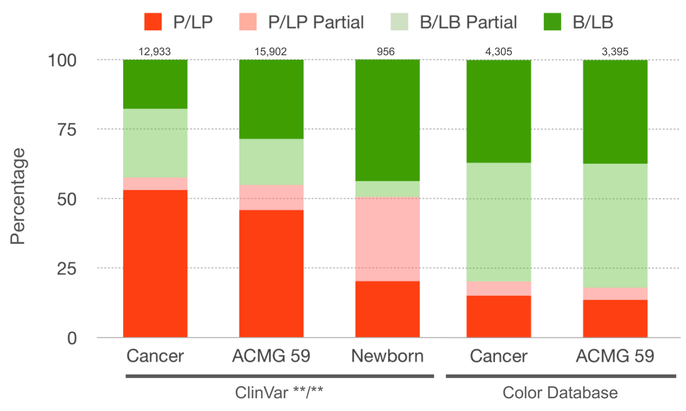
We first benchmarked our engine with a set of 9,159 variants for the BRCA1 an BRCA2 genes compiled from ClinVar (**/***) and the Color Genomics (https://data.color.com) databases. We also included a set of 830 variants from the VariSNPs database (Schaafsma and Vihinen, 2014, DOI: 10.1002/humu.22727) of presumably benign variants for the 15-gene Cancer panel.



To evaluate more thoroughly the performance of Fabric ACE, we analyzed a truth set of set of 37,491 variants for the three multi-gene panels we curated shown above. The number of variants analyzed from each source and panel is presented below.

Panel	ClinVar	Color Database	Totals
Cancer	12,933	4,305	17,238
ACMG 59	15,902	3,395	19,297
Newborn	956	N/A	956
Subtotals	*29,791*	*7,700*	*37,491*

Our current results show that Fabric ACE automatically classifies a high proportion of a truth set of ClinVar **/*** variants for the three panels we curated. This rate was slightly lower for the Color database possibly because the population screened is different to those in lab reports deposited to ClinVar. Notably, no misclassifications were observed. These results demonstrate that the engine can reduce dramatically the workload of clinical geneticists reviewing gene panel cases for clinical reporting.



VUS Reclassification

A challenge in clinical reporting is the need to reclassify variants as knowledge changes. We tested the ability of Fabric ACE to quickly reclassify BRCA1 and BRCA2 variants previously classified as VUS in a Japanese survey of breast cancer genes in patients and controls (Momozawa et al., 2018, DOI: 10.1038/s41467-018-06581-8) and in the Color database.

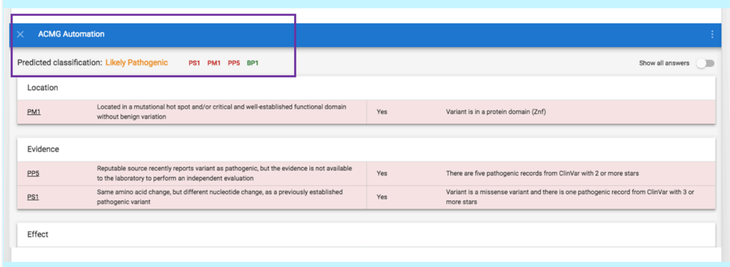
Source	Number of VUS	Reclassified P/LP	Reclassified B/LB	Reclassified (%)
Color DB	938	6	420	46%
Japan Data	127	2	168	44%

Our results demonstrate that Fabric ACE can quickly reprocess variants in the light of new information and could be very useful in reanalysis of previous cases and VUS reduction in a cost-effective fashion.

Implementation

We developed a natural language generation (NLG) module to provide the clinician the rationale for the final classification. This text is a reference for clinical geneticists when reviewing and signing-off cases, avoiding a black-box approach incompatible with clinical applications.

We embedded Fabric ACE within the variant scoring sheet of the clinical interpretation workflow of Fabric Enterprise. For panels where ACE is enabled, the predicted classification is shown together the text provided by the NLG module, highlighting the critical rules triggered for classification. In the case of variants where classification is incomplete, clinicians can leverage the partial answered rules and quickly complete manually those that will lead to a final variant classification.



CONCLUSIONS

- We demonstrate that Fabric ACE can automatically classify a high proportion of P/LP and B/LB ClinVar gold standard variants with no misclassifications, allowing clinical labs to save time and effort in processing panel tests.
- Unclassified variants are left with many criteria already answered by ACE to facilitate manual review for final classification.
- We also demonstrate quick automatic reclassification of variants previously designated as VUS, thus enabling reanalysis as clinical knowledge evolve.
- We integrated this engine into our cloud-based software platform for the analysis of NGS genomic tests: Fabric Enterprise.

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