Implementation of Vela Analytics to Accelerate Interpretation and Reporting of Next-Generation Sequencing-Based Oncology Testing in Clinical Diagnostic Laboratories

#316P

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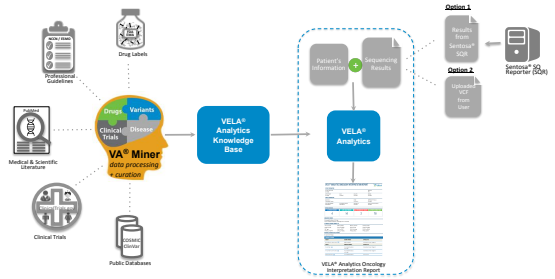
Introduction

Next-generation sequencing (NGS)-based diagnostics have demonstrated clinical utility in predicting survival benefits of targeted treatments in various cancer types. Tertiary analysis is a critical component in NGS workflow but its efficiency and accuracy have remained as the main challenges. Herein, we have developed Vela Analytics, a web-based software, that automates NGS data interpretation and reporting to facilitate timely clinical decision-making. Vela Analytics is compatible with any variant call format (VCF) file from any NGS instrument or gene panel to provide clinically actionable insights. As an integral part of Vela Oncology NGS workflow, it reports and interprets molecular information from OncoKey™ SL 60/525 Plus NGS Assays including single nucleotide variations (SNVs), insertions/deletions (INDELs), copy number variations (CNVs), fusion genes, spliced variants, oncogenic pathogens, microsatellite status as well as tumor mutation burden (TMB). Vela Analytics also provides evidence-based variants categorization according to AMP/ASCO/CAP guidelines.

Materials and Methods

Figure 1. Simplified Workflow of Vela Analytics Interpretation and Reporting



- Vela Analytics Knowledge Base contains information derived from:
  - ✓ FDA/EMA-approved drug labels
  - ✓ NCCN/ESMO clinical practice guidelines
  - ✓ Open clinical trials globally sourced from ClinicalTrials.gov
  - ✓ Peer-reviewed medical/scientific literature
  - ✓ Key public biomedical databases such as COSMIC, ClinVar, LOVD
- FDA/EMA-approved therapies, NCCN/ESMO guidelines, clinical trials and published literature are curated by a team with PhD in oncology.
- The Knowledge Base contains up-to-date and clinically actionable information with monthly updates of FDA/EMA drug labels and clinical trials.
- The input sequencing file in the form of VCF from a third party panel or from the sequencing results generated by *Sentosa*® SQ Reporter (Vela Diagnostics, Singapore).
- Two easy steps: upload a sequencing file with patient information and download the PDF report in as fast as 1 minute.
- Examples of Vela Analytics results were generated from the sequencing data of FFPE commercial reference standard (Horizon™ C3) and 14 FFPE clinical samples using the OncoKey™ SL 60/525 Plus NGS Assays.

Results

Table 1. Actionable genomic findings, immunotherapy biomarker findings, matched potential treatment options and oncoviral/oncobacterial findings were summarized in the table below. Various types of genomic alterations including SNVs, INDELs, CNVs, fusion genes, microsatellite status, TMB and oncogenic pathogens can be reported and comprehensively interpreted within 1-10 minutes (details not shown). Oncogenic pathogens were detected in 19H04355 and 19H11785.

No.	Sample ID	Tumor Type	Genomic Findings	Number/Category	Approved Therapied	Off-Label Therapies	Contraindicated Therapies	Potential Clinical Trials
1	10H02245	Non-Small Cell Lung Cancer	Actionable Variants	0	--	--	--	1
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
2	18H06019	Non-Small Cell Lung Cancer	Actionable Variants	3	--	3	--	23
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
3	19H08535	Non-Small Cell Lung Cancer	Actionable Variants	3	--	3	--	24
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive finding			--	
4	19H10117	Non-Small Cell Lung Cancer	Actionable Variants	2	--	3	0	19
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
5	19H10993	Non-Small Cell Lung Cancer	Actionable Variants	3	0	3	0	27
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
6	19H11639	Non-Small Cell Lung Cancer	Actionable Variants	5	3	2	0	66
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
7	14H00325	Thyroid Papillary Cancer	Actionable Variants	2	--	--	--	15
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
8	15H08296	Ovarian Cancer	Actionable Variants	43	4	1	0	61
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
9	18H04485	Ovarian Cancer	Actionable Variants	6	4	1	0	43
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
10	18H07841	Gastrointestinal Stromal Tumor	Actionable Variants	2	0	3	0	32
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
11	19H04459	Gastrointestinal Stromal Tumor	Actionable Variants	3	--	3	0	30
			Immunotherapy Biomarker	MSI-Low	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
12	19H04355	Head and Neck Cancer	Actionable Variants	6	0	5	0	38
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	HPV detected			--	
13	19H11785	Head and Neck Cancer	Actionable Variants	3	0	3	0	20
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	EBV detected			--	
14	19H09887	Colorectal Cancer	Actionable Variants	8	1	9	2	73
			Immunotherapy Biomarker	MS-Stable	--	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	
15	Horizon™ C3	Non-Small Cell Lung Cancer	Actionable Variants	23	2	10	0	215
			Immunotherapy Biomarker	TMB-High	2	--	--	
				MS-High	1	--	--	
			Oncoviral/Oncobacterial Findings	No positive findings			--	

No.	Tumor Type	Genomic Findings	Variant/ Category	Approved Therapied	Off-Label Therapies	Contraindicated Therapies	Potential Clinical Trials (66)
19H11639	Non-Small Cell Lung Cancer	Actionable Variants (5)	BRCA2 p.G602fs	--	Rucaparib Olaparib	--	11 Phase 2 1 Phase 1/2 5 Phase 1
			BRCA2 p.T3030fs	--		--	11 Phase 2 1 Phase 1/2 5 Phase 1
			DCBLD1/ROS1 fusion	Crizotinib (EMA) Entrectinib (FDA) Ceritinib (ESMO)	--	--	24 Phase 2 12 Phase 1/2 9 Phase 1
			MSH6 p.T1085fs	--	--	--	3 Phase 2 1 Phase 1 1 Phase 1
			REST/BRAF fusion	--	--	--	1 Phase 1
		Immunotherapy Biomarker	MS-Stable	--	--	--	1 Phase 1

Table 2. A wide range of therapeutics options suggested based on molecular profiling of non-small cell lung cancer patient 19H11639. Vela Analytics queries approved therapies across multiple regulatory agencies such as EMA, FDA and regional-specific oncology practice guidelines. Three TKIs were recommended based on the detected *ROS1* fusion. Off-label indications of two PARP inhibitors originally approved for other cancer types with deleterious *BRCA1/2* mutations were reported for this NSCLC patient. There are 66 open clinical trials that matched the detected NGS variants or the immunotherapy biomarker (Microsatellite Stable).

POTENTIAL CLINICAL TRIALS

INVESTIGATED THERAPIES	TRIAL DETAILS	MATCHING PATIENT BIOMARKERS
Atezolizumab	**A Modular Multi-Basket Trial to Improve Personalized Medicine in Cancer Patients (Basket of Baskets)** Phase 2 | Recruiting | NCT03767075 *Countries: France, Netherlands, Spain, Sweden, United Kingdom*	BRCA2 p.G602fs BRCA2 p.T3030fs MSH6 p.T1085fs

Figure 2. An example of potential clinical trial that matched the molecular findings. Investigational therapies, matched biomarkers and trial details including the title, phase, status and location of the trial are provided.

Gene	Alteration Type	Alteration	COSMIC ID	Support	Classification	Clinical Evidence
Tier 1: Variants with Strong Clinical Significance						
DCBLD1/ROS1	Fusion	DCBLD1-ROS1	-	3 (Reads)		Approved Therapy/Clinical Trial
BRCA2	Deletion	G602fs	COSV66449038	2.2% (VAF)	Pathogenic	Clinical Trial
BRCA2	Insertion	T3030fs	COSV66447774	2.89% (VAF)	Pathogenic	Clinical Trial
MSH6	Deletion	T1085fs	COSV52273658	4.96% (VAF)	Pathogenic	Clinical Trial
REST/BRAF	Fusion	REST-BRAF	-	4 (Reads)		Clinical Trial
Tier 2: Variants with Potential Clinical Significance						
No variant was found in this tier.						
Tier 3: Variants with Unknown Clinical Significance						
ARID1A	Deletion	P16del	COSV61387765	4.52% (VAF)	N.A.	Unknown
ARID1A	Deletion	PQ1326-1327del	COSV61371125	4.58% (VAF)	N.A.	Unknown
ARID1A	Deletion	G1848fs	COSV61371147	2.21% (VAF)	N.A.	Unknown
ROS1	SNV	S2229C	COSV63850786	97.25% (VAF)	N.A.	Unknown
ROS1	SNV	K2228Q	COSV63850793	100% (VAF)	N.A.	Unknown
ROS1	SNV	D2213N	COSV63850799	97.48% (VAF)	N.A.	Unknown
RET	SNV	G691S	COSV60687096	62.25% (VAF)	N.A.	Unknown
BRCA2	SNV	V2466A	COSV66451785	97.95% (VAF)	N.A.	Unknown

Table 3. Automatic variant categorization by in-house algorithm according to AMP/ASCO/CAP guidelines. Variants are classified into 4 tiers based on their clinical significance. Variants that predict response or resistance to approved therapies and variants that are investigated in well-powered clinical studies are classified into Tier I. Variants that predict response to approved therapies for a different tumor type and variants with pathogenic or likely pathogenic functions are classified into Tier II. NGS variants with matched approved therapies, off-label therapies or potential clinical trials are reported as actionable variants. For NSCLC patient 19H11639, 5 actionable variants were identified with matched treatment options.

ONCOVIRAL/ONCOBACTERIAL FINDINGS

HPV 16 Genotype (High risk)
E6/E7 DNA: Detected
E6/E7 RNA: Detected

Clinical Implications (Head and Neck Cancer - Squamous Cell Carcinoma)

HPV infection is an etiological factor for the development of head and neck squamous cell carcinoma (HNSCC), especially oropharyngeal cancer (PMID: 10793107; PMID: 18042931;

Figure 3. The high-risk HPV genotype 16 was identified in the head and neck tumor sample 19H04355 with positive detection of viral oncogenes E6/E7 in both DNA and RNA.

Conclusion

Vela Analytics can accurately transform rich genomic profiling data into clinically insightful and actionable outcomes by using an expertly curated knowledge base and a robust variant processing pipeline. Additionally, it identifies oncogenic pathogens to assess their association with cancer development, prognosis and treatment. Genomic findings and potential therapeutic options are comprehensively interpreted based on peer-reviewed clinical and scientific publications. As a decision support platform, it provides a rapid and cost-effective solution to assist timely decision making, empowering precision medicine in healthcare.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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