Framework for Genomic Biomarker Actionability and Use in Clinical Decision Making

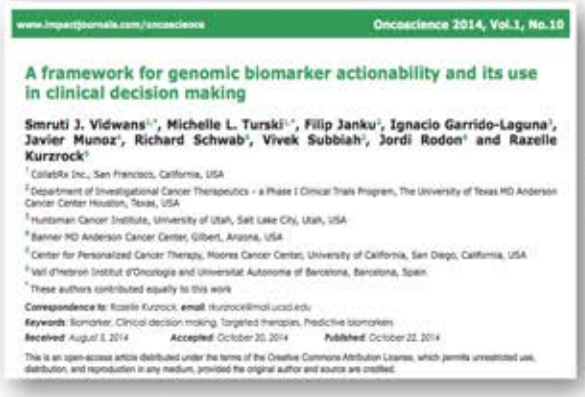
by Smruti Vidwans, PhD

ABSTRACT

As Next Generation Sequencing (NGS) is increasingly adopted into clinical practice, physicians are faced with the daunting task of identifying variants that are clinically actionable – those that can help them select potential treatment options - from a rapidly growing body of data. In oncology, tumor or liquid biopsies are profiled using NGS technologies to identify aberrations in cancer-related genes. Cancer panels range in size from a handful of genes to several hundred. Depending on the size of the NGS panel, many variants may be observed in tumors.

Clinical actionability is very contextual - it depends on many factors including diagnosis, nature of observed variant, targetability of variant by one or more drugs, evidence linking a variant to therapies and clinical trials as well as other considerations such as patient history and cancer phenotype. For physicians to be able to make the most informed treatment decisions based on NGS data, they will greatly benefit from transparency and insight into the contextual basis of variant actionability.

We have developed a two-dimensional clinical actionability framework that can be used to prioritize variants based on their targetability and evidence that links them to treatment options. In this poster, we will illustrate its usability in the clinical setting by showing how it could be used by physicians to interpret NGS test results in support of optimal patient care.



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A framework for genomic biomarker actionability and its use in clinical decision making

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Basis of actionability

Biomarker Criteria	Definition of Biomarker Criteria	Example*
Functional in driving the malignancy and can be targeted by approved drug(s)	Biomarker is a direct target of one or more approved drugs, and if targeting it will interfere with malignant cell growth.	ALK
Functional in driving the malignancy and can be targeted by investigational drug(s)	Biomarker is a direct target of one or more investigational drugs, and targeting it will interfere with malignant cell growth.	AKT1
Direct component of an actionable pathway that can be targeted by approved or investigational drugs	Biomarker may not be directly targeted by approved or investigational drugs, but instead is part of a pathway that drives the malignancy and can be directly targeted by drugs.	PTEN
Indirect component of an actionable pathway that can be targeted by approved or investigational drugs	Biomarker itself may not be directly targeted by approved or investigational drugs, but influences the activity or expression of other proteins that can be targeted by either approved and/or investigational drugs.	FBXW7
Homologous to an actionable biomarker that can be either directly or indirectly targeted by approved or investigational drugs	Biomarker itself may not be a target for clinically available drugs, but may be homologous to biomarkers that are targetable.	GNAO1
Can be targeted by drug(s) even if the biomarker is not itself functional in driving the malignancy	Biomarker may not be functionally important in the malignancy, yet can be expressed aberrantly or differentially in cancer cells and, hence, exploited for targeted delivery.	CD20, CD30

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Rationale for actionability

Biomarker Criteria	Definition of Biomarker Criteria	Example*
Drug approved with companion diagnostic	A drug is approved for cancers with an aberration in that biomarker.	BRAF, HER2, KIT
Therapeutic approach outlined in treatment guidelines (e..g NCCN guidelines)	Standard clinical treatment guidelines recommend that cancers with aberrations in that biomarker should (or should not) be treated with certain drugs and drug classes.	KRAS
Clinical evidence indicating responsiveness to drug class(es)	Available clinical data suggests that aberrations within the biomarker may be predictive of therapeutic response.	BRAF, PIK3CA, HER2, TP53
Clinical trials with biomarker aberration as an inclusion criteria	Clinical trials seek to enroll patients whose cancers harbor specific aberrations in that biomarker .	FBXW7
Pre-clinical evidence indicating responsiveness to drug class(es)	Available pre-clinical data suggests that aberrations within the biomarker may be predictive of therapeutic response.	MAP3K9
Evidence in genetic disease with biomarker aberration	Available clinical data on the therapeutic response of the biomarker within the context of a non-cancer disease.	TSC1
No evidence	A biomarker is **not** considered to be actionable if there is no data on the above mentioned criteria for that biomarker.	ADAMTS20[S2]

*See text for more information

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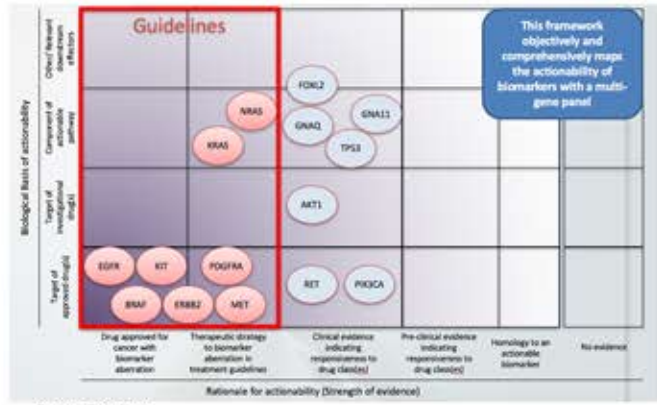
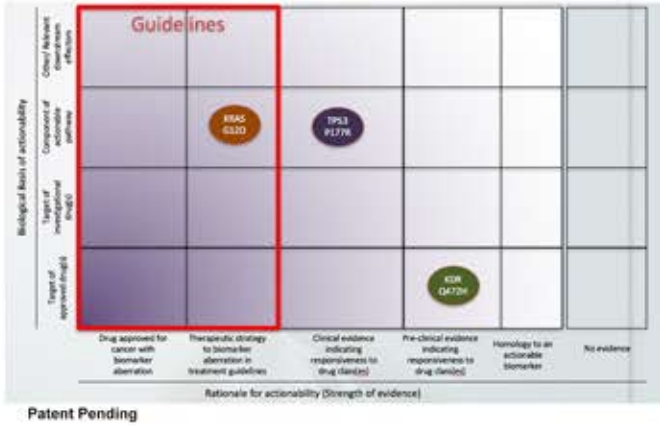
Actionability Framework in Action – Mapping of the Illumina TruSight Tumor 15



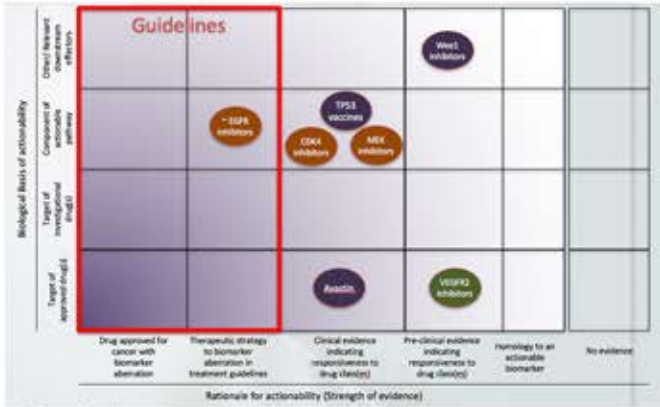
Patent Pending

Molecular Profile of Lung Adenocarcinoma Patient Mapped to Actionability Framework



Patent Pending

Potential Treatment Options Mapped to Actionability Framework



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CONCLUSIONS

The biomarker actionability framework can be used to:

Identify basis and rationale for actionability for genes to include into NGS panels for cancer(s)

Map & prioritize variants within a patient sample based on attributes such as strength of evidence for actionability

Map & prioritize potential treatment options relevant to variants based on strength of supporting evidence as well as approval status in diagnosis and other cancers

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