Molecular In My Pocket™

ONCOLOGY: *Interpretation of Genomic Assays*

INTERPRETATION OF GENOMIC ASSAYS – FREQUENTLY ASKED QUESTIONS

Genomic assay reports contain standardized terminology for genes, variants, transcripts, copy number changes, rearrangements, and allele frequencies. This reference card explains common elements of somatic-focused genomic reports and highlights practical questions to ask when interpreting variant findings or negative results in the context of assay design and analytical limitations.

What do the different symbols and numbers one sees in a genomic report mean?

Standardized nomenclature helps people with different training and experience and different laboratories to identify the same variant. Variants may be described at the protein level (*e.g.,* BRAF p.V600E), nucleotide (*e.g., BRCA1* c.5266dupC), or common legacy nomenclature. (*e.g. TERT* C228T promoter mutations or *EML4::ALK* fusion transcripts). The genomic location and transcript IDs are often included as universal references for additional clarity. *See below for examples.*

I am not familiar with the variant identified in the report. Where can I go for additional information?

In addition to any information issued in an interpretation (see below for a generic example) many online resources may be useful, including, , PubMed, Google Scholar, FDA.gov, and ClinicalTrials.gov. Advanced users may find databases such as COSMIC, CiVIC, Cancer Genome Interpreter, cBioPortal, and institutional or vendor-specific knowledgebases useful. *For additional assistance, please contact the laboratory or the molecular professional who issued the report.*

Will the assay detect the ABC variant in gene *XYZ*?

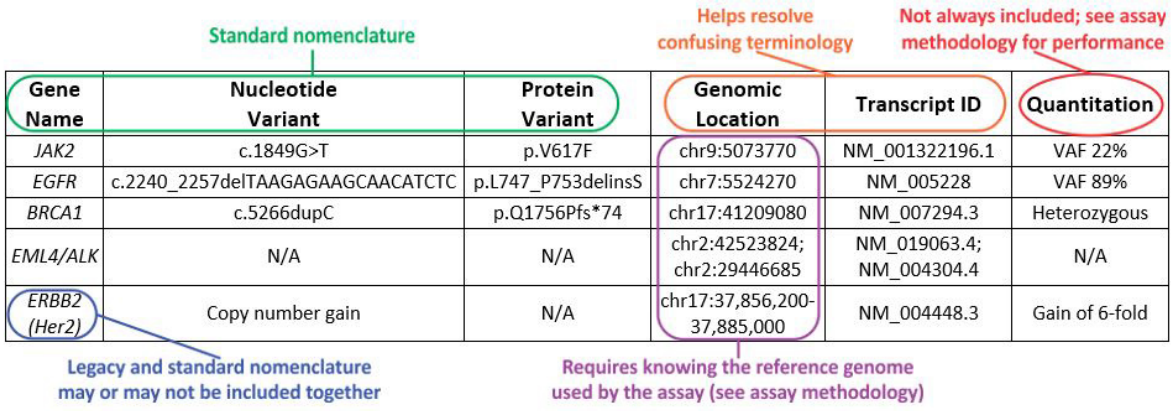
Check the assay description/details: Is the gene *XYZ* included on the panel? Is the targeted region, including the ABC variant, included on the panel? Does the assay detect this type of variant (*e.g.,* large indels or structural variants)? If it is a somatic ABC variant, was the assay designed to detect somatic alterations? If the assay does detect somatic alterations, what is the sensitivity (minimal Variant Allele Frequency, VAF) of the assay? *For additional assistance, please contact the laboratory or the molecular professional who issued the report.*

The report says there are no variants in gene *XYZ*. Could the assay have missed anything?

Every assay has limitations in its ability to detect all types of variants. There is always a lower limit of detection; moreover, genomic assays do not necessarily identify every type of variant with equivalent sensitivity. An assay may perform well in identifying single-nucleotide variants (SNVs), less well in identifying insertions and deletions (indels) and may not be able to identify larger copy number variants. *Negative results must always be interpreted with caution. And please always read assay information to understand the limitations of the assay.*

What is the significance of the Variant Allele Frequency (VAF)?

The VAF is the frequency at which the variant is detected in a specimen. It is often used as a proxy for disease burden. However, the VAF is affected by many factors including tumor purity, clonality, copy number state, specimen type, the variance of the assay , sampling, assay design, and cytogenetic changes at the allele including amplification or loss of heterozygosity (LOH). *The VAF should always be interpreted with caution*. *For additional assistance, please contact the laboratory or the molecular professional who issued the report.*



Gene Name	Nucleotide Variant	Protein Variant	Genomic Location	Transcript ID	Quantitation
JAK2	c.1849G>T	p.V617F	chr9:5073770	NM_001322196.1	VAF 22%
EGFR	c.2240_2257delTAAGAGAAGCAACATCTC	p.L747_P753delinsS	chr7:5524270	NM_005228	VAF 89%
BRCA1	c.5266dupC	p.Q1756Pfs*74	chr17:41209080	NM_007294.3	Heterozygous
EML4/ALK	N/A	N/A	chr2:42523824; chr2:29446685	NM_019063.4; NM_004304.4	N/A
ERBB2 (Her2)	Copy number gain	N/A	chr17:37,856,200-37,885,000	NM_004448.3	Gain of 6-fold

Example Interpretation: *XYZ* p.ABC: A single base substitution was detected in the *XYZ* gene, resulting in a missense variant. *XYZ* functions as a [tumor suppressor/proto-oncogene/other], regulating downstream cellular processes including ###. This variant occurs in the ### domain, altering the ability of the protein to ####, resulting in ####. The p.ABC variant confers a [better/worse] prognosis and is a target for FDA approved therapy, #######.

Methodology of the assay (the fine print) should include: The reference genome used (*e.g.* hg19/ GRCh37), target gene list, regions of genes covered (*e.g.,* entire coding region vs. hotspots), minimum mean depth of coverage, performance characteristics of the assay (lower limits of detection, maximum size of detectable indels, variance, etc.), and contact information for the laboratory.

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