

Molecular In My Pocket™

ONCOLOGY: Interpretation of Genomic Assays

INTERPRETATION OF GENOMIC ASSAYS – FAQs

What do all these different symbols and numbers mean?

Consistency in nomenclature helps people with different training and experience and different laboratories to identify the same variant. Variants may be identified by alteration to protein (e.g. *BRAF* p.V600E), nucleotide (e.g. *BRCA1* c.5266dupC), or non-standard 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) there are many online resources that may be useful, including MyCancerGenome.org, TCGA, PubMed, GoogleScholar, FDA.gov, and ClinicalTrials.gov. Advanced users may find databases such as COSMIC, CIVIC, or cBioPortal 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 - Is gene XYZ included on the panel? Is the region including the ABC mutation included on the panel? Does the assay detect this type of mutation (e.g., large indels or structural variants)? 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 indels at all. Negative results must always be interpreted with caution.

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 the variance of the assay (often as high as +/-15%), 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
<i>JAK2</i>	c.1849G>T	p.V617F	chr9:5073770	NM_001322196.1	VAF 22%
<i>EGFR</i>	c.2240_2257delTAAGAGAAGCAACATCTC	p.L747_P753delinsS	chr7:5524270	NM_005228	VAF 89%
<i>BRCA1</i>	c.5266dupC	p.Q1756Pfs*74	chr17:41209080	NM_007294.3	Heterozygous
<i>EML4/ALK</i>	N/A	N/A	chr2:42523824; chr2:29446685	NM_019063.4; NM_004304.4	N/A
<i>ERBB2 (Her2)</i>	Copy number gain	N/A	chr17:37,856,200-37,885,000	NM_004448.3	Gain of 6-fold

Standard nomenclature (points to Gene Name, Nucleotide Variant, Protein Variant)

Helps resolve confusing terminology (points to Genomic Location)

Not always included; see assay methodology for performance (points to Quantitation)

Legacy and standard nomenclature may or may not be included together (points to ERBB2 (Her2))

Requires knowing the reference genome used by the assay (see assay methodology) (points to Genomic Location)

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/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 the US-FDA approved therapy, #####.

Methodology of the assay (the fine print) should include: Reference genome used (e.g. hg19); 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.); contact information for the laboratory.



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