Variant Terminology for Clinical Trials

The Maine Cancer Genomics Initiative

Sponsored by: The Jackson Laboratory

Table 1: These are potential genetic variants or alterations that may be part of the eligibility for a clinical trial, and the alternate terminology you may find on a genomic test report.

Variant	Synonymous Terms	Examples	Meaning
Amplification	• Copy number gain • Gain	• ERBB2 Amplification/Amp • ERBB2 Copy Number Gain/Gain	An increase in the number of copies of a gene. *Not the same as overexpression.*
Deletion	• Copy Number Loss • Loss	• SMAD4 Copy Number Loss/Loss • PTEN del	A loss or deletion of the entire gene. *Not the same as a mutation.*
Fusion	• Rearrangement	• KIF5B-RET chromosomal rearrangement • KIFB5B-RET Fusion • RET gene rearrangement detected	Two genes that have been broken and fused together. *Not the same as a mutation.*
Gain	• Amplification • Copy number gain	• ERBB2 Amplification/Amp • ERBB2 Copy Number Gain/Gain	An increase in the number of copies of a gene. *Not the same as overexpression.*
Loss	• Copy number loss • Deletion	• CDKN2A Copy Number Loss/Loss • CDKN2A del	A loss or deletion of the entire gene. *Not the same as a mutation.*
Variant/ Mutation	• Splice site variant • Missense substitution • Nonsense substitution • Small insertion • Small deletion • Frameshift variant • Duplication	• CDH1 splice site 1565+1G>C • BRAF V600E • TP53 p.Q331* • EGFR exon 20 insertion • APC c.4463delT • TSC2 G654fs • SMAD3 c.546dupT	A change or variant in the sequence of a gene. This can change the function of the gene.
Rearrangement	• Fusion	• KIF5B-RET chromosomal rearrangement • KIFB5B-RET Fusion • RET gene rearrangement detected	Two genes have been broken and fused together. *Not the same as a mutation.*
Overexpression*	• RNA overexpression • Protein overexpression (IHC)	• ERBB2 (HER2) overexpressed* • ER (protein/IHC) positive 2+	Excessive expression of a gene may lead to too much of the RNA or protein being created. *Not the same as Amplification/Gain.*
Underexpression	• RNA under expression • Protein under expression or negative (IHC)	• ERBB2 (HER2) underexpressed* • HER2 negative 0* • HER2 negative 1+*	Lack of expression of a gene that may lead to too little of the RNA or protein being created. *Not the same as Deletion/Loss.*
Wildtype (WT)	• Alteration not detected • Negative for variant • Pertinent negatives	• KRAS wildtype • No reportable alterations: KRAS • KRAS variant/mutation not detected	The typical form of the gene. No changes or variants were detected in the gene.

**The gene ERBB2 creates the protein HER2.*

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Table 2: Some clinical trials will designate that the variant must be an inactivating or activating variant. Here are some general rules for identifying if a variant is activating or inactivating.

Variant	Types of Variants	Examples	Meaning
Activating variant/ mutation	• Gain of function variants • Copy number gains • Amplifications • Missense variants (some) • Fusions (some)	• PIK3CA p.E542K - GOF • EGFR Copy Number Gain • FGFR1 amp • MET Y1230H • TMPRSS2-ERG fusion	A variant that causes the gene to gain or increase its function.
Inactivating variant/ mutation	• Loss of function variants • Frameshift variants (most) • Nonsense variants (most) • Stop gain variants (most) • Splice site variants (most) • Start site variants	• PRKN c.413-1G>A - LOF • TP53 p.C124fs • NF1 S1766* • TP53 p.Q331* • CDH1 splice site 1565+1G>C • BRCA1 p.M1?	A variant that causes the gene to lose its function.

Some test reports will spell out if the variant is a gain or loss of function where the variant is identified. Others may have this information in the section of the report that talks in more detail about the gene and its function. If it is unclear, you may need to contact the testing company.

Table 3: Variants that may not qualify for clinical trial eligibility. Further investigation may be required if you are considering these for clinical trial enrollment.

Gene Alteration	Meaning
Variants of unknown/uncertain biological significance (VUS)	There was a variant identified in the gene, but it is uncertain that this variant causes any impact to the function of the gene. These will typically be in their own section on the test report.
Variants of equivocal amplification	There is some evidence of an increased number of copies of the gene, but not enough copies to call it a definitive amplification. Will be clearly marked as “equivocal”.
Variants designated as subclonal	A mutation that is present in a subset of tumor cells in a tumor sample or biopsy. Will be clearly marked as “subclonal”.
Variants noted to be indeterminate/insufficiently analyzed	There was not enough sample to adequately analyze these genes, so it is unknown if there are variants in these genes. These are not typically reported on test reports.
Benign variant	There was a variant identified in the gene, but it does not impact in the function of the gene. These are not typically reported on test reports.