alamya health

A Future Where Precision Medicine is the Standard

Variant Interpretation

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VARIANT INTERPRETATION

Variant interpretation is performed using a variety of tools. Variants of potential clinical significance are reported based on known or potential disease and phenotype associations, population frequency, and functional predictions. Copy number and structural variants are prioritized by known clinical relevance, predicted variant effect, population frequency, and known or putative disease-gene associations.

Variant classification is performed according to the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) guidelines and recommendations from the Clinical Genome Resource (ClinGen) (PMID: 25741868).

Primary findings:

Primary findings are variants (pathogenic, likely pathogenic, and VUS [variants of uncertain significance]) that are related to the indication for testing. Primary findings are returned for three categories of variants:

1. Variants related to the patient's phenotype: variants in genes with known or putative associations with human diseases that are consistent with the patient's phenotype.
2. Variants possibly related to the patient's phenotype: variants in genes with known or putative associations with human diseases but whose contribution to the patient's phenotype is uncertain based on available evidence.
3. Variants in candidate disease genes: variants in genes without known associations with human disease but with clinical, functional, and/or predictive evidence suggesting a possible role.

Medically actionable variants:

Medically actionable variants are unrelated to the indication for testing. Pathogenic or likely pathogenic variants are returned for genes associated with disorders for which health management strategies of surveillance or intervention have been defined (https://www.alamyahealth.com/wp-content/uploads/2025/01/MAV_Dec-30-2024.pdf).

Incidental findings:

Incidental findings are pathogenic or likely pathogenic variants inadvertently discovered during the process of data analysis but unrelated to the indication for testing and for which health management strategies of surveillance or intervention have been defined.

Pharmacogenomic findings:

Pharmacogenomic findings are genomic variants that influence drug metabolism, drug efficacy, and drug toxicity. The variants selected for analysis and reporting are based upon strong and consistent scientific evidence linking them to defined drug responses and for which the benefits clearly outweigh the risks (https://www.alamyahealth.com/wp-content/uploads/2025/04/PGx_Variants_Mar2025-.pdf). The variants are converted to the reported alleles using RxMax as licensed from Nalagenetics PTE LTD. Guidance regarding the use of this information is provided via reference to the PharGKB and CPIC databases.

Carrier findings:

Carrier findings are pathogenic or likely pathogenic variants in genes associated with a serious childhood onset genetic condition. These findings, which are helpful for reproductive planning, are generally without health concerns for the individual tested (https://www.alamyahealth.com/wp-content/uploads/2025/01/Carrier_Dec-30-2024.pdf).

DNA methylation findings

DNA methylation variants are distinct, well-established genome-wide methylation patterns (aka methylation signatures or episignatures) and/or localized methylation changes that are characteristic of specific disorders. These methylation patterns are identified either by manual inspection of that particular region of the genome or by use of EpigenCentral, a machine learning platform that analyzes DNA methylation data to identify and classify epigenetic signatures associated with rare genetic and neurodevelopmental disorders (https://www.alamyahealth.com/wp-content/uploads/2025/05/Methylation-signature-screening-April-2025.pdf).

Repeat alteration findings:

Repeat alteration findings reported are pathogenic repeat alterations, i.e., outside the range seen in healthy individuals and for which the repeat variant is established to cause disease (https://www.alamyahealth.com/wp-content/uploads/2025/01/Repeat_variants_18Jan2025v3.pdf). The repeat alteration variants are identified by manual inspection and by use of EPI2ME/wf-human-variation (v2.6.0).

Polygenic risk findings:

Polygenic risk findings are combinations of genomic variants in many genes that influence risk for developing common disorders such as breast cancer and atherosclerotic cardiovascular disease. In combination with age, sex, family history, lifestyle information, and genetic ethnicity, these variants can be used to compute a relative risk of developing disease. Currently risk scoring is available to women for breast cancer and atherosclerotic cardiovascular disease and to men for atherosclerotic cardiovascular disease. The risk scores are respectively calculated using the MammoReady and CardiacReady as licensed from Nalagenetics PTE LTD.