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Abstract Topic:- Molecular and cytogenetic diagnostics

Abstract Title:- Re-classification of BRCA VUS variants in cancer patients – A Boon or Bane?

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Aims:-To Reclassify all the variants across the BRCA germline and Somatic samples tested

Methods:- Study setting – Central Molecular diagnostics and Laboratory (CMDL), Apollo Main Hospitals, Greams Road, Chennai.

Type of study - Retrospective Observational Study

Study period - January 1st 2018 to Sep 30th 2023

Sample size: 360 (Germline - 262 & Somatic – 98)

Inclusion criteria – All cases sent for Germline and Somatic BRCA testing

Exclusion criteria – Cases sent for other NGS panels

Methodology: The study was carried out for both germline and somatic BRCA assays performed on Ion Personal Genome Machine (PGM) with an Ion 318 chip (Life Technologies) following the manufacturer's instructions. The annotated VCF files from the IR were used for reclassifying the VUS. Reclassification of all variants were carried out by using an orthogonal software/in silico prediction tools based on the current ACMG and AMP guidelines for Germline and Somatic variants classification respectively. Variants of Uncertain significance were compared with RENOVO machine learning algorithm.

Results:- The percentage of VUS calls were high in somatic assay (12.24%) when compared to germline assay (10.30%) in this study. Variant reclassification was not available for 40.75% and 16.66% of germline and somatic variants respectively. The majority of reclassified variants were downgraded for both germline and somatic cases studied respectively (37.04%, 58.38%). Of the germline reclassified variants, 37.04% were reclassified to benign, 3.7% to low probability benign, 7.4% to likely pathogenic, and 11.11% to pathogenic. Of the reclassified somatic variants, 33.34% were reclassified to benign, 25.04% to Likely benign, 16.66% to low probability pathogenic, 8.33% to pathogenic.

Conclusions:- BRCA1/2 variants may be reclassified over time. Reclassification of BRCA VUS poses many ethical and practical challenges related to recontacting and counselling patients. Data sharing is essential to improve variant interpretation, to help patients receive appropriate care based on their genetic results.

Keywords:- NGS,BRCA,RENOVO, Reclassification