Poster 12: Evaluating the Association Between Family Cancer History and Variants of Uncertain Significance

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Topic
Genetics

Objectives
This study examines the correlation between the presence of variants of uncertain significance (VUS) and a positive family history of cancer in first-degree relatives.

Methods
A retrospective data analysis was conducted from November 2017 to September 2024 on 9,059 patients from 65 clinical locations across California and Hawaii who underwent genetic testing and had documented family cancer history. Patients were categorized based on the cancer history of their first-degree relatives, including breast, ovarian, pancreatic, prostate, colorectal, endometrial, kidney, and gastric cancers. Additional groupings were made for those with family histories of multiple cancers, such as multi-BRCA-related cancers, multi-Lynch-related cancers, and general multi-cancer family histories.

Results
Among the cohort, 2,749 tested patients had a VUS with a detection rate of 30.3%. No statistically significant associations were observed between VUS status and a positive family history of any single cancer type in first-degree relatives (all p-values > 0.05, ranging from $p = 0.118$ for breast cancer to $p = 0.535$ for pancreatic cancer). Similarly, a multi-cancer family history did not show statistical significance (all p-values > 0.05, ranging from $p = 0.129$ for multi-BRCA-related cancers to $p = 0.703$ for multi-Lynch-related cancers). These findings indicate that having a first-degree relative with a history of these cancers does not correlate with the likelihood of carrying a VUS. A deeper dive specifically into the BRCA1 and BRCA2 VUS patients also showed no statistical significance in relation to BRCA-related cancers in the family ($p = 0.129$).

Conclusions
Therefore, our results show there is no significant relationship between family history and VUS results in patients tested. Mersch et al found that 91.2% of VUS are downgraded into benign polymorphisms, which would indicate that they are not clinically significant. These findings suggest that VUS occurrence may be independent of hereditary cancer patterns, highlighting the need for cautious interpretation in genetic counseling.