ATM and *PALB2* Variant Curation Guidelines Progress Update: ClinGen Hereditary Breast, Ovarian, and Pancreatic Cancer Variant Curation Expert Panel

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Introduction: Variant classification for hereditary breast, ovarian, and pancreatic cancer (HBOP) genes is complicated by multifactorial etiology of cancer and incomplete penetrance, causing lack of consensus in variant classification. To address discrepancies, the ClinGen Hereditary Breast, Ovarian and Pancreatic Variant Curation Expert Panel (HBOP VCEP) is developing gene-specific modifications of the ACMG/AMP sequence variant classification guidelines (ACMG/AMP SVI), starting with *ATM* and *PALB2*.

Methods: The HBOP VCEP focuses on variant interpretation guidance for HBOP genes (*ATM, PALB2, CHEK2, RAD51C, RAD51D, BRIP1,* and *BARD1)*. HBOP VCEP members meet monthly to review if ACMG/AMP SVI criterion should be adopted, modified, or omitted for each gene. Next, pilot variants are evaluated using the agreed upon gene-specific guidelines. The ClinGen Sequence Variant Interpretation Group provides feedback and approves final rules.

Results: To adjust ACMG/AMP *ATM* and *PALB2* variant classification rules, 4/28 original ACMG/AMP codes were accepted, whereas 7/28 were modified with gene specifications. A further 5/28 and 4/28 codes were clarified with disease specifications and 12/28 and 13/28 codes were omitted for *ATM* and *PALB2*, respectively. A pilot classification of 33 *ATM* variants classified 12 pathogenic (P), 4 likely pathogenic (LP), 6 variant of uncertain significance (VUS), 2 likely benign (LB), and 9 benign (B) variants. Prior to this review, 11/33 variants had conflicting or uncertain classifications in ClinVar (2 Conflicting LP/VUS; 4 Conflicting B/LB/VUS; 5 VUS). In addition, 40 *PALB2* variants were classified, 14 P, 6 LP, 12 VUS, 3 LB, and 5 B, and 13/40 variants had conflicting or uncertain classifications in ClinVar (3 Conflicting LP/VUS; 3 Conflicting B/LB/VUS; 7 VUS).

Conclusion: Standards for variant evaluation for *ATM* and *PALB2* were developed to provide guidance on variant classification and clarify discrepant variant classifications. Resolution of uncertain and discrepant classifications is crucial for maximizing diagnostic yield and appropriately managing cancer surveillance and treatment.