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

Megan Holdren MS, CGC, Marcy E. Richardson PhD, Deborah Ritter PhD, Colin Young PhD, Terra Brannan PhD, Tina Pesaran MS, CGC, Lauren Zec MS, CGC, Susan Hiraki MS, CGC, Michael Anderson PhD, Melissa Southey PhD, Clare Turnbull MD, PhD, Marc Tischkowitz MD, PhD, Huma Rana MD, MPH, Shannon McNulty Gray PhD, Sean Tavtigian PhD, Logan Walker PhD, William D. Foulkes PhD, Alvaro N.A. Monteiro PhD, Sarah Brnich MD, PhD, Melissa Cline PhD, Amanda B. Spurdle PhD, Miguel de la Hoya PhD, Fergus J. Couch PhD

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Introduction: Recommendations for individuals with suspicious personal and family histories of cancer traditionally include germline testing of cancer predisposition genes. Variant classification for hereditary breast, ovarian, and pancreatic cancer genes is complicated by multifactorial etiology of cancer and incomplete penetrance, causing a lack of consensus in classification of many variants. Classification of variants of uncertain significance (VUS) as pathogenic or benign and resolution of discrepant classifications in ClinVar are crucial for maximizing diagnostic yield and appropriately managing cancer surveillance and treatment. To supersede differences in classification between diagnostic laboratories and further clarify variants of uncertain significance, 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 for hereditary breast, ovarian, and pancreatic cancer genes, including *ATM* and *PALB2*.

Methods: The focus of the HBOP VCEP is on classification of variants in the non-*BRCA1/2*, non-mismatch repair (MMR) associated breast, ovarian and pancreatic cancer predisposition genes *ATM, PALB2, CHEK2, RAD51C, RAD51D, BRIP1,* and *BARD1*. The HBOP VCEP members meet monthly to review ACMG/AMP sequence variant classification guidelines in the context of a single gene to determine the extent to which each classification criterion should be adopted, modified, or omitted. *ATM* and *PALB2* were evaluated first by the group due to the abundance of gene-specific data available in the literature. Once variant classification rules were developed, pilot variants were evaluated using the agreed upon gene-specific guidelines. The ClinGen Hereditary Cancer Clinical Domain Working Group (HC-CDWG) reviewed, provided feedback, and approved final rules and pilot variant classifications.

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 labeled as not applicable due to gene specific considerations for variant classification for *ATM* and *PALB2*, respectively. The *ATM* variant classification rules were finalized by the HBOP VCEP and approved by the HC-CDWG in early 2022. *PALB2* rules were finalized in late 2022. A pilot classification of 33 *ATM* variants classified 12 as pathogenic (P), 4 as likely pathogenic (LP), 6 as VUS, 2 as likely benign (LB), and 9 as benign. Prior to this review, 11/33 of these variants had conflicting classifications in ClinVar or were considered VUS (2 Conflicting LP/VUS; 4 Conflicting B/LB/VUS; 5 VUS). In addition, 40 *PALB2* variants were classified, 12 P, 6 LP, 15 VUS, 2 LB, and 4 B. Before the pilot study, 10/40 of these variants had conflicting classifications in

ClinVar or were classified as a VUS (2 Conflicting LP/VUS; 3 Conflicting B/LB/VUS; 5 VUS). Curation of other *ATM* and *PALB2* variants with discrepant classifications in ClinVar is ongoing.

Conclusion: Standards for gene-specific variant evaluation for *ATM* and *PALB2* were developed by an international group of experts in hereditary cancer genetics to provide guidance on future variant classification and clarify discrepant variant classifications across diagnostic laboratories and research groups. The HBOP VCEP will continue to review non-*BRCA1/2*, non-MMR associated breast, ovarian and pancreatic cancer predisposition genes to provide recommendations on variant classification. Most importantly, continued collaboration between experts in hereditary breast, ovarian, and pancreatic cancer genetics will aid in accurate, informative hereditary cancer genetic test results for patients.