**Title**: ClinGen HBOP VCEP curation of ATM variants associated with Ataxia-Telangiectasia

**Authors:** Marcy E. Richardson* PhD[1], Terra Brannan PhD[1], Susan Hiraki MS, CGC[2], Megan Holdren MS, CGC[3], Huei San Leong PhD[4], Victor Martinez MSc, PhD[5], Yu Mei MD[6], Akila S. Shanmugasundaram MTech[7], Shofia Souceradjou BSc[7], Colin Young PhD[1], Lauren Zec MS, CGC [8], Fergus J. Couch PhD[3]
[1]Ambry Genetics, [2]GeneDx, [3]Mayo Clinic, [4]Peter MacCallum Cancer Centre, [5] IWK Health, [6] Boston Children's Hospital, [7] Zifo Genomics Research Institute, [8] Natera

**Introduction**: ClinGen Hereditary Breast, Ovarian, and Pancreatic Cancer Variant Curation Expert Panel (HBOP VCEP) created modified American College of Medical Genetics/Association of Molecular Pathology variant curation rules specific to ATM. After guideline development, trained biocurators performed curation of ATM variants using the rules and submitted classifications to ClinVar for community use. The ATM rules specify that Ataxia-Telangiectasia (A-T) variants also cause cancer predisposition; therefore, the biocurator group elected to focus on clinically relevant interpretations by prioritizing variants reported in A-T patient cohorts. A-T case data informs the PM3 code, which required consideration of patient phenotype, phase of the variants, classification of the second variant, and considerations to avoid double-counting patients reported multiple times in the literature.

**Methods**: Literature reports of A-T cases were identified via HGMD disease search. Manuscripts with the largest cohort were prioritized. An initial set of 21 A-T-associated variants from one publication were classified using the HBOP VCEP ATM guidelines. Papers were annotated in VCEP internal tracking systems by biocurators and reviewed at biocurator meetings to ensure consistent PM3 application. Annotations included documenting study laboratory methods, definition of phenotype, method of phase determination (if any), and other study-specific details relevant to the application of PM3. PM3 was modified based on the ATM HBOP VCEP rules (number of cases, phenotype details, phase data, and classification of second variants).

**Results**: Of the A-T-associated variants, 17 were classified as pathogenic (P), 2 as likely pathogenic (LP), and 2 as variants of uncertain significance (VUS). PM3 for the variants was applied at varying weight (4 PM3_very strong, 7 PM3_strong, 5 PM3, and 5 PM3_supporting). Without the A-T case data applied, the final classifications would have been 11 P, 5 LP, and 5 VUS variants.

**Conclusion**: Application of phenotype-specific criteria (PS4 or PP4) is excluded within the HBOP VCEP ATM specified rules. Breast cancer is common with a high degree of genetic heterogeneity and phenocopy. A-T case data allows for application of PM3 at variable weights to classify ATM variants, clarifying classifications for heterozygous carriers with cancer risk as

well as individuals with A-T. The HBOP VCEP continues to submit FDA-approved ATM variant classifications to ClinVar.