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## CCMG STATEMENT ON GERMLINE VARIANT CLASSIFICATION

### CCMG Laboratory Practice Committee:

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Approved by the CCMG Board of Directors: April 3, 2017

Purpose & Document Development: The Canadian College of Medical Geneticists' Laboratory Practice Committee has reviewed the recommendations regarding classification of sequence variants as published by the ACMG, the Association for Molecular Pathology (AMP), and the College of American Pathologists working group in Richards *et al.*, "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology." *Genetics in Medicine* **17**, pp 405–423 (2015).

Recommendations: The committee broadly endorses these guidelines, which are already in use at many centres in Canada. The committee felt that there would be no incremental benefit to drafting a separate set of guidelines for use by Canadian centres, as the requirements for objective proof of pathogenicity for sequence variants is universal. The committee agreed that differences of interpretation were most likely to arise when evidence was insufficient or unavailable, making it difficult or impossible to prepare evidence-based guidelines that would solve such differences.

The CCMG Laboratory Practice Committee noted that the ACMG guidelines were specifically designed for "...interpretation of variants observed in patients with suspected inherited (primarily Mendelian) disorders in a clinical diagnostic laboratory setting..." and specifically "...not intended for the interpretation of somatic variation..." nor "...to fulfill the needs of the research community in its effort to identify new genes in disease."

The CCMG Laboratory Practice Committee specifically notes the importance of consultation between laboratory specialists and referring clinician(s), including consideration of family history, phenotypic details, and results from other diagnostic investigations to aid clinical interpretation of variants.

Lastly, as part of fully endorsing these recommendations, Canadian centres are encouraged to participate in the submission and/or publication of sequence variants identified to appropriate curated databases or journals as much as possible, and to the extent possible under specific-provincial and national privacy laws, to ensure the cumulative evidence of variant frequency and associated clinical phenotype(s) is publicly available and accessible to diagnostic labs.