Advances in high-throughput next-generation sequencing (NGS) have led to rapid expansion of clinical lab test categories which now include traditional single gene or targeted tests as well as gene panels, exome and genome sequencing. As a result, variant interpretation in clinical labs has become increasingly challenging due to the large number of variants generated by NGS, the complexity of the tests and lacks of standards for assessing variants. The recently updated (2015) ACMG/AMP guidelines for variant interpretation in Mendelian disorders provide framework guidance for the standardization of variant classification. However, numerous excises following the new guidelines still showed considerable inter or intra lab inconsistencies. It is expected that the framework guidelines should be optimized and expanded to be more detailed in order to meet the specific challenges in a particular clinical setting.

We formed a variant interpretation subcommittee which is made up of ABMGG molecular directors who sign out cases in the area of carrier testing, Sanger sequencing, disease gene panels and exome sequencing within our clinical laboratory. The subcommittee held regular meetings to evaluate the guidelines as well as review a list of challenging variants encountered during routine case sign-out and submitted by lab directors and genetic counselors. In addition to the criteria and rules in the published ACMG/AMP guidelines, information from the literature, ClinVar, internal databases and public variant databases etc. were also gathered and experts were consulted as needed. During the meetings new variant classification criteria and rules were proposed, discussed and established in order to resolve real life interpretation dilemmas and internal variant classification discordance.

Version one of the modified guidelines include six additional criteria, with four in the strong evidence (PS) category and two in the moderate evidence category (PM).

Those additions are mostly to address the evidence of mosaicism, multiple occurrences of de novo events for the same variant, effect of different sizes of in-frame changes and multiple truncating events within the same exon or functional domain.

### Conclusion

The refined guidelines have been shown to help minimize internal report inconsistencies and improve variant interpretation quality and efficiency. As expected, there are instances of different lab directors interpreting the same variant differently that cannot be resolved even applying the modified guidelines. In order to address this type of challenges, rules of using the lower (or higher, depending on the nature of the tests) category should be established to ensure that within a clinical lab consistent variant classifications is reported out to clinicians.