4.3. Improving Genetic Testing for Cardiac and Thoracic Aortic Diseases in a Diagnostic Laboratory

Lucas Bronicki, PhD, FACMG, DABMGG

Cardiomyopathies and thoracic aortic aneurysms and dissections (TAADs) harbour a strong genetic component and substantially increase the risk of sudden death. Cardiomyopathies, classically categorized as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC), and TAADs are groups of disorders affecting the structure and function of the heart and thoracic aorta, respectively. Advancements in our understanding of the genetic causes of cardiomyopathies and TAADs are rapidly evolving, with an increasing number of associated genes emerging every year. This, in turn, causes strain on genetic diagnostic laboratories, which must try to keep pace with advancements in the field to provide testing with high analytical and clinical validity. At the CHEO Genetics Diagnostic Laboratory (GDL), we have implemented workflows that facilitate keeping our cardiomyopathy and TAAD next generation sequencing (NGS) testing relevant and accurate, without severely depleting resources. Two of these workflows include biennial revisions of our cardiomyopathy and aortopathy NGS testing menus and implementing current gene- and disease-specific variant interpretation guidelines. Both workflows rely heavily on guidelines and recommendations set by the Clinical Genome Resource (ClinGen), an organization comprising of international clinical, laboratory and research experts in genetic diseases. Following these workflows for our HCM NGS testing reduced the number of genes offered from 19 to 12 and decreased the general population frequency threshold used for variant interpretation. In addition to increasing efficiencies in the laboratory, these changes decreased the number of inconclusive results by ~62% combined, without affecting the diagnostic yield. Our data reaffirms that workflows aimed at updating gene testing menus and variant interpretation guidelines lead to improved analytical and clinical validity, and ultimately improved patient care.

Educational objectives:

By the end of the presentation, participants will be able to
1. Explain the need to regularly update gene panels and variant interpretation methodologies for diagnostic tests, particularly cardiomyopathies and TAADs.

2. Apply the workflows implemented by the CHEO GDL to maintain or improve analytical and clinical validity for cardiomyopathies and TAAD testing.

3. Discuss how these strategies ultimately lead to improved patient care.