Title: Exploring the Yield of RASopathy Variants in Individuals with Presumed Nonsyndromic Hypertrophic Cardiomyopathy

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Abstract: Hypertrophic Cardiomyopathy (HCM) is the most common inherited cardiomyopathy and is characterized by left ventricular hypertrophy (LVH) without other systemic or acquired causes of LVH. RASopathy conditions that present with LVH are often diagnosed in childhood, yet their phenotypic heterogeneity and attenuation of noticeable physical features can hinder correct diagnosis in adults presumed to have nonsyndromic HCM. Because there are distinct medical management differences between RASopathy-associated HCM and nonsyndromic HCM, the inclusion of RASopathy genes on genetic testing panels ordered for patients with presumed nonsyndromic HCM may have significant clinical utility.

Few studies have commented on the yield of RASopathy gene variants among genetic testing orders in this patient population. Our work aimed to evaluate the relevance of including RASopathy genes in genetic testing panels for adults with presumed nonsyndromic HCM. Through a joint collaboration between a commercial genetic testing laboratory and an academic medical institution, we obtained de-identified data from adults with presumed nonsyndromic HCM who were found to have a RASopathy gene variant identified through cardiac genetic testing panels. The panels included an HCM-specific panel, a cardiomyopathy-specific panel, a cardiomyopathy and arrhythmia panel, and a customizable cardiology-centric panel.

The data were analyzed using descriptive statistics, and the diagnostic yields for pathogenic and likely pathogenic (P/LP) RASopathy variants detected by both the combined cardiac panels and the HCM-specific panel were assessed. Thirteen individuals had a P/LP variant in a RASopathy gene across panels, with a yield of 0.092% when including all aforementioned panels and 0.267% when including only HCM-specific panel test orders. PTPN11 had the highest number of detected P/LP variants (n=7), followed by SOS1 (n=3). SOS1 had the highest number of detected variants of uncertain significance (n=31), followed by RAF1 (n=30).

Most RASopathy gene variants were detected on the HCM-specific panel. Overall, the majority of RASopathy genes included on the panels had no detected variants. These findings revealed an overall low yield of P/LP RASopathy gene variants, with detectable P/LP variants found in only a subset of genes (PTPN11, RAF1, RIT1, SOS1, and LZTR1). Notably, SOS1 had the second highest number of detected P/LP variants, though current clinical

guidance for HCM genetic testing does not comment on the inclusion of SOS1 gene analysis. Based on our findings, further consideration about which RASopathy genes are beneficial to include on HCM panels, specifically regarding SOS1, is warranted.