Title: Estimating Sensitivity of the International Gastric Cancer Linkage Consortium's (IGCLC) 2020 Hereditary Diffuse Gastric Cancer (HDGC) Genetic Testing Criteria

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Background: Hereditary diffuse gastric cancer (HDGC) is an autosomal-dominant syndrome characterized by early-onset diffuse gastric cancer (DGC) and lobular breast cancer (LBC), and most closely associated with mutations in the *CDH1* gene. The International Gastric Cancer Linkage Consortium (IGCLC) recently updated its criteria for genetic testing, most notably by expanding the total number of criteria to nine and relaxing age restrictions. The purpose of this study was to evaluate the ability of the IGCLC's updated criteria to identify carriers of *CDH1* pathogenic variants.

Methods: Personal and family histories were reviewed for a cohort of consecutive *CDH1* mutation carriers identified by multi-gene panel testing, independent of HDGC clinical criteria. The percentage of subjects meeting the IGCLC 2015 and 2020 criteria were calculated. These calculations were performed twice, once without making any assumptions about missing pathology, and once assuming gastric cancer to be diffuse when pathology was not available. For comparison, we also calculated the percentage of subjects captured by our own proposed alternative criteria for *CDH1* genetic testing (Table 1).

Results: Histories of 111 *CDH1* mutation carriers and their 649 family members were reviewed. When making no assumptions about missing pathology, a small (18%) and equal percentage of *CDH1* mutation carriers met the IGCLC 2015 and 2020 genetic testing criteria. When assuming unspecified gastric cancer to be diffuse, 44/111 (40%) subjects met the 2015 criteria and 52/111 (47%) met the 2020 criteria. 7/8 (88%) of the additional subjects meeting the updated criteria did so because of the increase in the age cutoff for an individual with DGC from 40 to 50. 93/111 (84%) of subjects met our proposed alternative criteria.

Conclusions: The updated IGCLC genetic testing criteria for HDGC are marginally more sensitive for capturing *CDH1* mutation carriers than previous iterations, but they are also more cumbersome. Unavailable cancer pathology reports of family members are not only a limitation of our dataset, but also a frequent real-world obstacle to the proper application of the IGCLC criteria. Our proposed criteria both address this issue and offer significantly greater sensitivity than the new IGCLC criteria.