Phenotypes of Patients with *APC* Gene Mutations Identified via Multi-gene Cancer Panel Testing

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Background: Familial adenomatous polyposis (FAP) is an autosomal dominant colorectal cancer syndrome resulting from germline mutations in the adenomatous polyposis coli (*APC*) gene. Classic FAP is characterized by the presence of >100 adenomatous colorectal polyps, often presenting in childhood, with an extremely high likelihood of progression to colorectal cancer. Attenuated familial adenomatous polyposis (AFAP) typically presents with 10 to <100 adenomatous colorectal polyps. We hypothesize that mutation carriers identified on multi-gene panel tests (MGPT) are more likely to present with a milder phenotype.

Methods: We performed a retrospective review of patients undergoing MGPT at a single laboratory from 6.7.2012 through 12.3.2015 who were found to harbor either a pathogenic or likely pathogenic variant in the *APC* gene (*APC*+). Individuals harboring *APC* p.I1307K were excluded. Clinical histories were evaluated from test request forms (TRF).

Results: A total of 127 *APC*+ patients were identified. Ninety of 127 (70.1%) met the current National Comprehensive Cancer Network (NCCN) *APC* testing criteria of ≥10 adenomatous polyps; 9 of the 127 (7.1%) did not meet NCCN *APC* testing criteria; 8 of the 127 (6.3%) did not technically meet testing criteria but had a personal and/or family history indicative of FAP/AFAP; 20 of the 127 (15.7%) had inadequate clinical or family history data provided on the TRF to allow for assessment. Seventy-two of 90 patients met NCCN *APC* testing criteria based on the number of adenomatous polyps. Of those, 33 (45.8%) had >100 adenomatous polyps; 31 of 72 (43.1%) had 20-99 adenomatous polyps; and 8 of 72 (11.1%) had 10-19 adenomatous polyps. Overall, 85/127 (66.9%) had a history of cancer, including 40 colorectal cancers and 16 breast cancers, two of which were male breast cancers.

Conclusions: 7.1% of *APC*+ patients did not meet current NCCN *APC* testing guidelines. Additionally, 54.2% of positives presented with fewer than 100 polyps suggesting that mutation carriers identified on MGPT may be more likely to present with AFAP. Interestingly, 13% of mutation carriers with clinical data available had a breast cancer diagnosis, including 2 male breast cancers. More investigation is required to determine if these breast cancers are associated with the *APC* mutation or if they are sporadic.