Title: NF1 Mutations Detected on Multi-gene Cancer Panel Testing in Probands with Atypical Phenotypes

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Neurofibromatosis 1 (NF1) is a highly penetrant hereditary condition, with the majority of NF1 patients meeting clinical diagnostic criteria in childhood. Women with NF1 are estimated to have an approximate 4 to 8-fold increased risk of developing breast cancer as well as an increased risk for other cancers. As such, the *NF1* gene has recently been included in multi-gene cancer panels. The purpose of this study was to assess the phenotypes of individuals in our hereditary cancer panel cohort carrying a pathogenic *NF1* mutation. Multi-gene hereditary cancer panels with *NF1* gene alterations reported from October 2013 through April 2013 were reviewed. Retrospective test requisition form review was used to obtain clinician-reported clinical history information for individuals with pathogenic *NF1* mutations. Ten individuals were identified to carry a pathogenic *NF1* mutation. Upon review, 6 were noted to have a clinical diagnosis of NF1 on the test requisition forms. Mutations in this group included 3 missense, 2 nonsense, and 1 frameshift. The remaining 4 individuals were not noted to have a clinical diagnosis of NF1 or other NF1-related features on the test requisition forms, nor were their family members. The absence of an NF1 clinical diagnosis and NF1-related features was confirmed by a follow-up phone call to the clinicians for all 4 cases. Mutations in this group included 2 nonsense, 1 frameshift, and 1 splicing. Clinical histories of these 4 cases included three patients diagnosed with breast cancer, two >50y and one <50y, and one unaffected patient. Of note, the unaffected patient also carried the *APC* I1307K moderate risk mutation and has a family history of colon cancer. Identification of pathogenic NF1 mutations in individuals with atypical phenotypes via a multi-gene panel approach may help expand upon the clinical indications currently used for NF1 testing. Further research is needed on atypical phenotypes in the NF1 population and the potential impact on clinical management for NF1 patients and their family members.