TITLE: Hereditary Mutations in Colorectal Cancer: More than Meets the Diagnostic Eye

Meyer A, McFarland R, Dalton E, LaDuca H.

PURPOSE: Approximately 5-10% of colorectal cancer (CRC) has a hereditary basis. The clinical availability of hereditary multi-gene panel testing (MGPT) allows for CRC patients to be tested concurrently for common hereditary CRC syndromes such as Lynch syndrome, familial adenomatous polyposis (FAP), and MUTYH-associated polyposis (MAP), along with rare CRC syndromes such as juvenile polyposis syndrome (JPS). This study aimed to assess the prevalence of hereditary mutations among CRC patients undergoing MGPT and to describe the clinical histories and impact of the genetic test results for those with mutations detected.

METHODS: Clinical histories and genetic test results were reviewed for CRC patients who underwent MGPT between March 2012 and December 2014. MGPTs ranged in size from 5 to 49 genes. The mutation-positive CRC cohort was then analyzed to determine if patients met the National Comprehensive Cancer Network's (NCCN) diagnostic testing criteria for the respective syndrome (v1.2015).

RESULTS: Of 2,555 CRC patients analyzed by MGPT, 268 (10%) were found to carry a pathogenic mutation or likely pathogenic variant. The majority of mutation-positive individuals (62%) harbored mutations in genes associated with Lynch syndrome (46%; n=124), FAP (6%; n=17), and MAP (9%; n=24). The remaining 38% (n=103) had a mutation detected in one of 17 other hereditary cancer genes, including *CHEK2* (n=31), *TP53* (n=10), *BRCA1* (n=*10),* and *BRCA2* (n=11). NCCN diagnostic testing criteria were available for 13 of the 24 genes in which a pathogenic mutation was identified (see table). Of individuals with mutations in one of the five genes associated with Lynch syndrome, 91% met NCCN testing criteria. For those with mutations in *APC* or biallelic *MUTYH* mutations, FAP/MAP criteria for testing or to "consider testing" were met by 37% (n=15/41). Overall, 42% (n=17/40) of individuals with mutations in non-Lynch/FAP/MAP genes met NCCN testing criteria for the associated syndrome, including 3 of 7 *BMPR1A* or *SMAD4* mutation carriers*,* 0 of 2 *CDH1* mutation carriers, 3 of 10 *TP53* mutation carriers, and 12 of 21 *BRCA1/2* mutation carriers.

CONCLUSION: Results from this study demonstrate the ability of MGPT to identify hereditary mutations in CRC patients who may have otherwise evaded diagnosis of both common and rare CRC syndromes based on current testing guidelines. This is supported by the observation that only 37% of those with *APC* or biallelic *MUTYH* mutations met testing criteria for FAP/MAP and only 44% of individuals with mutations in non-Lynch/FAP/MAP genes met NCCN testing criteria for the associated syndrome. The utilization of MGPT increases the identification of CRC patients who may not otherwise be tested and allows them to benefit from increased screening and prophylactic surgery to reduce their risks of cancer.

Syndrome	Gene(s)	Mutations Detected, N	Meets NCCN Criteria	
			n	%
Lynch syndrome	*MLH1/MSH2/MSH6/ PMS2/EPCAM*	124	113	91
Familial adenomatous polyposis	*APC*	17	6	35
MUTYH-associated polyposis	*MUTYH (biallelic)*	24	9	37.5
Juvenile polyposis	*SMAD4/BMPR1A*	7	3	43
Li-Fraumeni syndrome	*TP53*	10	3	30
Hereditary Diffuse Gastric Cancer	*CDH1*	2	0	0
Hereditary Breast and Ovarian Cancer	*BRCA1/BRCA2*	21	12	57
	Total	205	146	71
	CHEK2	38	N/A	
	ATM	8		
	PALB2	4		
	MRE11A	3		
	RAD50	3		
	NBN	2		
	RAD51C	1		
	BRIP1	1		
	BARD1	1		
Familial Atypical Mole-Malignant Melanoma	*CDKN2A*	1		
Neurofibromatosis, type 1	*NF1*	1		
	Total	268		