Supplementary Online Content

Pearlman R, Frankel WL, Swanson B, et al. Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. *JAMA Oncol*. Published online December 15, 2016. doi:10.1001/jamaoncol.2016.5194.

This supplementary material has been provided by the authors to give readers additional information about their work.

Prevalence and spectrum of germline cancer susceptibility gene mutations among early-onset colorectal cancer patients

ON-LINE ONLY SUPPLEMENTAL MATERIAL

eTable 1. Ohio Colorectal Cancer Prevention Initiative Participating Hospitals			
Hospital	**City**	**Hospital**	**City**
Akron General Medical Center	Akron	Wright-Patterson Medical Center	Dayton
Summa Akron City/St. Thomas Hospital	Akron	Grady Memorial Hospital	Delaware
Summa Barberton Hospital	Barberton	Mercy Fairfield Hospital	Fairfield
Mercy Clermont Hospital	Batavia	Blanchard Valley Regional Health Center	Findlay
Aultman Hospital	Canton	Wayne Hospital	Greenville
Mercy Medical Center	Canton	Fairfield Medical Center	Lancaster
Adena Health System	Chillicothe	St. Rita's Medical Center	Lima
Bethesda North Hospital- TriHealth	Cincinnati	MedCentral Health System	Mansfield
Good Samaritan Hospital- TriHealth	Cincinnati	Marietta Memorial Hospital	Marietta
Mercy Anderson Hospital	Cincinnati	Marion General Hospital	Marion
Mercy West Hospital	Cincinnati	St. Luke's Hospital[a]	Maumee
The Christ Hospital	Cincinnati	Hillcrest Hospital	Mayfield Heights
The Jewish Hospital	Cincinnati	Atrium Medical Center	Middletown
Cleveland Clinic Foundation	Cleveland	Knox Community Hospital	Mount Vernon
Fairview Hospital	Cleveland	Licking Memorial Hospital	Newark
MetroHealth System	Cleveland	Southern Ohio Medical Center	Portsmouth
Doctors Hospital West	Columbus	Robinson Memorial Hospital	Ravenna
Grant Medical Center	Columbus	Springfield Regional Medical Center	Springfield
Mount Carmel East	Columbus	ProMedica Flower Hospital	Sylvania

Mount Carmel West	Columbus	ProMedica Toledo Hospital	Toledo
Ohio State University	Columbus	Toledo Clinic Cancer Center	Toledo
Riverside Methodist Hospital	Columbus	Upper Valley Medical Center	Troy
Summa Western Reserve	Cuyahoga Falls	South Pointe Hospital	Warrensville Heights
Good Samaritan Hospital	Dayton	Mount Carmel St. Ann's	Westerville
Kettering Medical Center	Dayton	Genesis Healthcare System	Zanesville
Miami Valley Hospital	Dayton		

[a]Participation ended 12/31/2015

eTable 2. Variants of Uncertain Significance									
Patient #	**Sex**	**Age**	**Colon cancer site**	**Clinical history**	**MMR tumor status**	**Gene**	**Nucleotide change**	**Protein change**	**Additional pathogenic mutation**
369352	Female	39	Rectosigmoid junction		Proficient	*APC*	7.5kb deletion promoter1A		
366535	Male	40	Cecum		Deficient[a]	*APC*	c.295C>T	p.R99W	
398305	Female	47	Sigmoid		Proficient	*APC*	c.1243G>A	p.A415T	
369365	Female	30	Ascending		Proficient	*APC*	c.1606G>A	p.E536K	
449571	Female	39	Cecum		Proficient	*APC*	c.1825G>A	p.V609I	
362916	Male	46	Rectum		Proficient	*APC*	c.2209T>C	p.Y737H	
362971	Male	48	Left colon		Proficient	*APC*	c.3352A>G	p.N1118D	*BRCA2* c.5946del, p.S1982Rfs*22
455734	Female	32	Cecum		Proficient	*APC*	c.3650A>C	p.N1217T	
448728	Female	44	Sigmoid		Proficient	*APC*	c.3653C>T	p.T1218M	
363017	Female	49	Rectosigmoid junction		Proficient	*APC*	c.4325C>G	p.P1442R	*APC* c.1213C>T, p.R405X
362916	Male	46	Rectum		Proficient	*APC*	c.4919G>A	p.R1640Q	
400625	Male	49	Sigmoid		Proficient	*APC*	c.5879C>T	p.P1960L	
417730	Female	44	Splenic flexure		Proficient	*APC*	c.6363_6365 dupTGC	p.A2122dup	
451469	Male	40	Transverse		Proficient	*APC*	c.6473C>G	p.P2158R	
426470	Male	29	Sigmoid		Proficient	*APC*	c.6782C>T	p.P2261L	
500601	Male	47	Rectum		Proficient	*APC*	c.7174C>T	p.P2393S	
456269	Female	49	Cecum		Proficient	*APC*	c.7832C>T	p.T2611I	
410925	Male	37	Sigmoid	Thyroid cancer 39	Proficient	*APC*	c.8182G>A	p.V2728M	
362983	Female	43	Sigmoid		Proficient	*APC*	c.8261G>A	p.S2754N	
366727	Female	32	Rectum		Proficient	*ATM*	c.712A>G	p.I238V	
441033	Female	45	Rectum		Proficient	*ATM*	c.1138T>A	p.Y380N	
418764	Female	31	Rectum		Proficient	*ATM*	c.2096A>G	p.E699G	
365403	Male	37	Transverse		Deficient	*ATM*	c.2260C>A	p.Q754K	*PMS2* c.1831dup, p.I611Nfs*2
430326	Male	45	Ascending		Proficient	*ATM*	c.2770C>T	p.R924W	
453447	Female	41	Ascending		Proficient	*ATM*	c.2804C>T	p.T935M	

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Patient #	**Sex**	**Age**	**Colon cancer site**	**Clinical history**	**MMR tumor status**	**Gene**	**Nucleotide change**	**Protein change**	**Additional pathogenic mutation**
450179	Female	39	Sigmoid		Proficient	*ATM*	c.3151G>C	p.E1051Q	
448651	Male	40	Rectosigmoid junction		Deficient[a]	*ATM*	c.3781A>G	p.I1261V	
413049	Female	49	Left colon		Proficient	*ATM*	c.4256_4258 delinsCTT	p.L1419_L1420 delinsPF	
369721	Female	44	Not specified		Proficient	*ATM*	c.4362A>C	p.K1454N	
414440	Female	47	Rectosigmoid junction		Proficient	*ATM*	c.4402G>A	p.V1468I	
365576	Female	47	Cecum		Proficient	*ATM*	c.4424A>G	p.Y1475C	
435516	Female	43	Rectum		Proficient	*ATM*	c.4534G>A	p.A1512T	
402047	Male	47	Hepatic flexure		Proficient	*ATM*	c.4687G>A	p.D1563N	
500396	Female	43	Rectum		Proficient	*ATM*	c.4724G>A	p.R1575H	
448728	Female	44	Sigmoid		Proficient	*ATM*	c.4768C>T	p.L1690F	
450705	Male	33	Hepatic flexure		Proficient	*ATM*	c.5228C>T	p.T1743I	
365558	Male	47	Cecum		Proficient	*ATM*	c.5278A>G	p.M1760V	
500396	Female	43	Rectum		Proficient	*ATM*	c.6820G>A	p.A2274T	
453934	Female	37	Rectum		Proficient	*ATM*	c.7122A>T	p.E2374D	
364086	Female	44	Splenic flexure		Proficient	*ATM*	c.7381C>T	p.R2461C	
459709	Female	34	Ascending		Deficient	*ATM*	c.7390T>C	p.C2464R	Constitutional *MLH1* promoter methylation
434678	Male	47	Sigmoid		Proficient	*ATM*	c.7492T>G	p.S2498A	
364392	Female	34	Rectosigmoid junction		Deficient	*ATM*	c.7592T>C	p.M2531T	*MLH1* c.1279C>T, p.Q427X
454645	Female	40	Rectum		Proficient	*ATM*	c.7618G>A	p.V2540I	
451474	Male	43	Ascending		Proficient	*ATM*	c.8129A>G	p.K2710R	
362913	Male	47	Transverse		Proficient	*ATM*	c.8261C>T	p.T2754I	
410926	Male	39	Rectum		Proficient	*ATM*	c.9086G>A	p.G3029D	
416288	Female	45	Rectum		Proficient	*ATM*	exon 61-62 dup		
423987	Female	46	Hepatic flexure		Proficient	*ATM*	exon 61-62 dup		

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Patient #	**Sex**	**Age**	**Colon cancer site**	**Clinical history**	**MMR tumor status**	**Gene**	**Nucleotide change**	**Protein change**	**Additional pathogenic mutation**
455498	Male	48	Rectum		Proficient	*BARD1*	c.33G>T	p.Q11H	
457640	Male	48	Ascending		Proficient	*BARD1*	c.568G>A	p.A190T	
390026	Female	44	Left colon		Proficient	*BARD1*	c.773T>C	p.I258T	
453292	Female	43	Sigmoid		Proficient	*BARD1*	c.841C>T	p.P281S	
404905	Female	47	Ascending		Proficient	*BARD1*	c.1314G>A	p.K438K	
362917	Male	31	Sigmoid		Proficient	*BARD1*	c.1429G>A	p.V477M	
369365	Female	30	Ascending		Proficient	*BARD1*	c.2191C>G	p.R731G	
453612	Male	34	Ascending		Proficient	*BARD1*	c.2209A>G	p.I737V	
435548	Female	39	Sigmoid		Proficient	*BMPR1A*	c.995T>C	p.L332P	
450705	Male	33	Hepatic flexure		Proficient	*BMPR1A*	c.1058A>G	p.Q353R	
407850	Female	47	Rectosigmoid junction		Proficient	*BMPR1A*	c.1433G>A	p.R478H	
440168	Male	42	Rectum		Proficient	*BRCA2*	c.620C>T	p.T207I	
418764	Female	31	Rectum		Proficient	*BRCA2*	c.3194T>C	p.I1065T	
388606	Female	39	Rectosigmoid junction		Proficient	*BRCA2*	c.6792G>C	p.L2264F	
458435	Female	37	Rectum		Proficient	*BRCA2*	c.6817A>G	p.R2273G	
364010	Male	47	Sigmoid		Proficient	*BRCA2*	c.8204C>G	p.P2735R	
362916	Male	46	Rectum		Proficient	*BRCA2*	c.8417C>T	p.S2806L	
248119	Male	39	Cecum		Proficient	*BRCA2*	c.9206G>T	p.C3069F	*SMAD4* c.430_431del, p.S144Rfs*7
416287	Female	43	Sigmoid	Breast cancer 42	Proficient	*BRCA2*	c.9608A>G	p.Y3203C	
404530	Male	48	Cecum		Deficient	*BRIP1*	c.139C>G	p.P47A	*MSH2* c.942+3A>T
404445	Female	48	Sigmoid		Proficient	*BRIP1*	c.316C>T	p.R106C	
429807	Female	32	Rectum	Thyroid cancer 32	Proficient	*BRIP1*	c.317G>A	p.R106H	*APC* c.1759del, p.S587Afs*3
366716	Male	33	Right colon		Deficient	*BRIP1*	c.485G>A	p.R162Q	*MLH1* c.200G>A, p.G72E
500685	Male	34	Ascending		Deficient	*BRIP1*	c.628C>T	p.P210S	*MLH1* c.1381A>T, p.K461X
451255	Male	44	Rectosigmoid junction		Proficient	*BRIP1*	c.790C>T	p.R264W	
458453	Male	48	Rectum		Proficient	*BRIP1*	c.1871C>T	p.S624L	

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Patient #	**Sex**	**Age**	**Colon cancer site**	**Clinical history**	**MMR tumor status**	**Gene**	**Nucleotide change**	**Protein change**	**Additional pathogenic mutation**
429729	Male	48	Rectosigmoid junction		Proficient	*BRIP1*	c.2220G>T	p.Q740H	
416373	Male	43	Transverse		Proficient	*BRIP1*	c.2440C>T	p.R814C	
369568	Female	45	Rectum		Proficient	*BRIP1*	c.3079G>A	p.E1027K	
413103	Male	49	Sigmoid		Proficient	*BRIP1*	c.3104G>A	p.R1035H	
500601	Male	47	Rectum		Proficient	*BRIP1*	c.3149C>A	p.T1050N	
426530	Female	22	Transverse		Proficient	*BRIP1*	c.3378A>C	p.E1126D	
456891	Male	49	Ascending, Ascending	Synchronous primaries	Proficient	*CDH1*	c.88C>A	p.P30T	
406767	Male	32	Sigmoid		Proficient	*CDH1*	c.88C>A	p.P30T	
454110	Female	46	Ascending		Proficient	*CDH1*	c.1138-3C>T		
409270	Female	46	Not specified		Proficient	*CDH1*	c.2074G>A	p.A692T	
443428	Male	47	Sigmoid		Proficient	*CDH1*	c.2165-15C>A		
369574	Male	49	Rectum		Proficient	*CDH1*	c.2371C>T	p.L791F	
419770	Female	45	Sigmoid		Proficient	*CDH1*	c.2398C>T	p.R800C	
369732	Female	45	Not specified		Proficient	*CDH1*	c.2590G>A	p.E864K	*PALB2* exon 11 deletion
458435	Female	37	Rectum		Proficient	*CDK4*	c.245G>A	p.R82Q	
435548	Female	39	Sigmoid		Proficient	*CDKN2A*	c.-33G>C		
445556	Male	46	Sigmoid	Prostate cancer 45	Proficient	*CDKN2A*	c.-34G>C		
363008	Male	43	Not specified		Proficient	*CDKN2A*	c.217A>C	p.S73R	
457689	Male	28	Rectum		Proficient	*CDKN2A*	c.369T>A	p.H123Q	
369345	Female	43	Rectosigmoid junction		Proficient	*CDKN2A*	c.430C>T	p.R144C	
451469	Male	40	Transverse		Proficient	*CHEK2*	c.-6G>A		
453528	Male	47	Sigmoid		Proficient	*CHEK2*	c.61C>A	p.P21T	
440170	Male	45	Sigmoid		Proficient	*CHEK2*[†]	c.470T>C	p.I157T	*MUTYH* c.1187G>A, p.G396D
452296	Male	48	Sigmoid		Proficient	*CHEK2*[†]	c.470T>C	p.I157T	
450268	Male	44	Rectum		Proficient	*CHEK2*[†]	c.470T>C	p.I157T	
393250	Male	46	Rectum		Proficient	*CHEK2*[†]	c.470T>C	p.I157T	
429729	Male	48	Rectosigmoid junction		Proficient	*CHEK2*[†]	c.470T>C	p.I157T	

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Patient #	**Sex**	**Age**	**Colon cancer site**	**Clinical history**	**MMR tumor status**	**Gene**	**Nucleotide change**	**Protein change**	**Additional pathogenic mutation**
448624	Female	42	Sigmoid	Thyroid cancer 42	Proficient	*CHEK2*[f]	c.470T>C	p.I157T	
417427	Male	44	Sigmoid		Proficient	*CHEK2*	c.539G>A	p.R180H	
72270	Female	39	Cecum		Proficient	*CHEK2*	c.592+3A>T		
442447	Male	46	Rectum		Proficient	*CHEK2*	c.593-20_593-18del		
409270	Female	46	Not specified		Proficient	*CHEK2*	c.661A>G	p.L221V	
448307	Female	47	Rectum		Proficient	*CHEK2*	c.751A>T	p.I251F	*BRCA2* c.1755_1759del, p.K585Nfs*3
455368	Female	31	Rectum		Proficient	*CHEK2*	c.1091T>C	p.I364T	
455905	Female	38	Rectum		Proficient	*CHEK2*	c.1336A>G	p.N446D	
451469	Male	40	Transverse		Proficient	*CHEK2*	c.1343T>G	p.I448S	
369568	Female	45	Rectum		Proficient	*CHEK2*	c.1343T>G	p.I448S	
442888	Male	20	Ascending		Proficient	*CHEK2*	c.1343T>G	p.I448S	
408570	Female	48	Cecum		Deficient	*MLH1*[e]	c.207+5G>C		
442522	Female	47	Sigmoid		Proficient	*MLH1*	c.1887A>T	p.E629D	
418090	Female	49	Sigmoid		Proficient	*MLH1*[f]	c.1897-2A>G		
363001	Female	39	Transverse, Rectum	Synchronous primaries	Proficient	*MSH2*	c.80C>A	p.P27Q	
364370	Female	46	Rectum	Colon cancer 28	Deficient	*MSH2*	c.80C>T	p.P27L	*MLH1* c.2252_2253delAA, p.K751Sfs*3
366413	Male	48	Ascending, Splenic flexure, Sigmoid	Synchronous primaries (3)	Deficient	*MSH2*	c.557A>G	p.N186S	*MSH2* c.2096C>A, p.S699X
365558	Male	47	Cecum		Proficient	*MSH2*	c.894G>C	p.Q298H	
430190	Male	37	Hepatic flexure		Deficient	*MSH2*[d]	c.1832T>A	p.V611E	
434827	Female	44	Rectosigmoid junction	Multiple polyps	Proficient	*MSH6*	c.257C>T	p.T86I	
445718	Male	42	Descending		Deficient	*MSH6*[c]	c.1109T>C	p.L370S	
409370	Female	46	Sigmoid		Proficient	*MSH6*	c.1211A>G	p.N404S	
438833	Female	47	Sigmoid		Proficient	*MSH6*	c.1915G>A	p.E639K	

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449664	Female	42	Sigmoid		Proficient	*MSH6*	c.3203G>A	p.R1068Q	
456049	Female	42	Cecum		Proficient	*MSH6*	c.3649A>G	p.R1217G	
448624	Female	42	Sigmoid	Thyroid cancer 42	Proficient	*MUTYH*	c.607C>T	p.R203C	
409270	Female	46	Not specified		Proficient	*MUTYH*	c.625A>G	p.I209V	
362938	Male	39	Ascending	4 adenomas, multiple hyperplastic rectal polyps	Deficient[a]	*MUTYH*[b]	c.698G>A	p.G233D	*MUTYH* c.1187G>A, p.G396D
404905	Female	47	Ascending		Proficient	*MUTYH*	c.890G>A	p.R297K	
406808	Male	48	Rectosigmoid junction		Proficient	*MUTYH*	c.1435-17C>G		
362214	Female	37	Rectosigmoid junction		Proficient	*NBN*	c.-16del		
362998	Female	30	Sigmoid		Proficient	*NBN*	c.224G>C	p.G75A	
456140	Male	31	Sigmoid		Proficient	*NBN*	c.456G>A	p.M152I	
458035	Male	48	Rectum		Proficient	*NBN*	c.643C>T	p.R215W	
419770	Female	45	Sigmoid		Proficient	*NBN*	c.643C>T	p.R215W	
442888	Male	20	Ascending		Proficient	*NBN*	c.786C>A	p.F262L	
410248	Male	30	Ascending		Proficient	*NBN*	c.1222A>G	p.K408E	
365376	Male	39	Cecum		Proficient	*NBN*	c.1484C>T	p.P495L	
399411	Male	46	Rectum		Proficient	*NBN*	c.1720T>A	p.L574I	
453447	Female	41	Ascending		Proficient	*NBN*	c.1729G>T	p.D577Y	
423046	Male	49	Cecum		Proficient	*PALB2*	c.20A>G	p.K7R	
365554	Male	34	Sigmoid		Proficient	*PALB2*	c.110G>A	p.R37H	
455786	Female	36	Ascending, Ascending	Synchronous primaries	Proficient	*PALB2*	c.1213C>G	p.P405A	
423046	Male	49	Cecum		Proficient	*PALB2*	c.2057G>A	p.R686K	
448188	Female	46	Sigmoid		Proficient	*PALB2*	c.3073G>A	p.A1025T	
451255	Male	44	Rectosigmoid junction		Proficient	*PALB2*	c.3418T>G	p.W1140G	
365590	Female	43	Left colon		Proficient	*PALB2*	c.3449T>G	p.L1150R	
407851	Male	39	Rectum		Proficient	*PALB2*	c.3449T>G	p.L1150R	
448650	Male	38	Rectum		Proficient	*PMS2*	c.149G>A	p.G50D	

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423828	Male	49	Ascending		Deficient	*PMS2*[a]	c.215G>A	p.G72E	
426810	Male	41	Cecum		Deficient	*PMS2*	c.322G>T	p.G108W	*APC* c.3920T>A, p.I1307K
458448	Male	47	Rectosigmoid junction		Proficient	*PMS2*	c.884G>A	p.R295Q	
369365	Female	30	Ascending		Proficient	*PMS2*	c.1199A>C	p.Q400P	
426530	Female	22	Transverse		Proficient	*PMS2*	c.1280G>A	p.R427H	
369787	Male	46	Rectum		Proficient	*PMS2*	c.1715C>T	p.A572V	
406585	Female	48	Right colon		Proficient	*PMS2*	c.1723A>G	p.N575D	
417591	Male	44	Transverse		Deficient	*PMS2*	c.2149G>A	p.V717M	*MLH1* c.589-2A>G
423527	Female	44	Sigmoid		Proficient	*PMS2*	c.2149G>A	p.V717M	
406585	Female	48	Right colon		Proficient	*PMS2*	c.2386G>A	p.V796I	
434829	Female	48	Sigmoid		Proficient	*PMS2*	c.2438G>T	p.R813L	
453509	Male	39	Rectum		Proficient	*PMS2*	c.2438G>T	p.R813L	
417427	Male	44	Sigmoid		Proficient	*PTEN*	c.78C>T	p.T26T	
453447	Female	41	Ascending		Proficient	*PTEN*	c.210-7_210-3del		
365168	Male	37	Sigmoid		Proficient	*RAD51C*	c.730A>G	p.I244V	
401998	Female	37	Ascending, Transverse	Synchronous primaries	Proficient	*RAD51C*	c.790G>A	p.G264S	
426973	Female	49	Ascending		Proficient	*RAD51C*	c.790G>A	p.G264S	
448723	Male	44	Rectum		Proficient	*RAD51C*	c.790G>A	p.G264S	
458632	Female	44	Rectosigmoid junction		Proficient	*RAD51D*	c.1A>G	p.M1?	
423191	Female	37	Rectosigmoid junction		Proficient	*RAD51D*	c.629C>T	p.A210V	
367050	Female	43	Cecum		Proficient	*RAD51D*	c.797G>A	p.R266H	
401998	Female	37	Ascending, Transverse	Synchronous primaries	Proficient	*SMAD4*	c.554C>A	p.P185Q	
364090	Female	46	Sigmoid	Thyroid cancer 40	Proficient	*SMAD4*	c.677C>T	p.A226V	
455786	Female	36	Ascending, Ascending	Synchronous primaries	Proficient	*STK11*	c.929G>A	p.R310Q	
402247	Female	38	Rectosigmoid		Proficient	*STK11*	c.1168G>A	p.V390M	

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Patient #	**Sex**	**Age**	**Colon cancer site**	**Clinical history**	**MMR tumor status**	**Gene**	**Nucleotide change**	**Protein change**	**Additional pathogenic mutation**
			junction						
404905	Female	47	Ascending		Proficient	*TP53*	c.173C>G	p.P58R	
417590	Male	38	Rectum		Proficient	*TP53*	c.800G>A	p.R267Q	

Abbreviations: MMR, mismatch repair
MMR deficient tumor = microsatellite instability and/or abnormal immunohistochemistry, MMR proficient tumor = microsatellite stability and/or normal immunohistochemistry
[a]Double somatic mutations explained MMR deficient tumor
[b]Variant reclassified to likely pathogenic after segregation analysis
[c]Variant reclassified to pathogenic after extensive segregation analysis
[d]Variant reclassified to likely pathogenic after somatic testing
[e]Variant reclassified to pathogenic after RNA studies
[f]The classification of pathogenicity of this mutation varies by laboratory

eTable 3. Genotypes and Phenotypes of Patients with a Hereditary Cancer Syndrome									
Patient #	**Sex**	**Age**	**Clinical history**	**MMR tumor status[f]**	**Gene**	**Nucleotide change**	**Protein change**	**Family history[b]**	**Met NCCN criteria[g]**
365557	Male	20	Known mutation in family.	Deficient	*MSH2*	c.1749dupT	p.I584Yfs*14	Father[a] colon 48; Pat. grandfather colon 67, pancreatic 81	Y
417965	Female	21	Polyposis. Known mutation in family.	Proficient	*APC*	c.2804dupA	p.Y935X	Mother[a] FAP; Mat. grandfather[a] colon 30s, FAP	Y
432465	Female	29		Deficient	*MSH2*	c.2152C>T	p.Q718X	Mother endometrial 52; Mat. grandmother ovarian 42; Pat. uncle pancreatic 66	Y
393829	Male	29	Polyposis. Known *APC* mutation.	Proficient	*APC*	c.2377C>T	p.Q793X	Father[a](*APC*) colon 20s, FAP; Mat. aunt cervical 24, multiple myeloma 50; Mat. grandmother colon and lymphoma 66; Mat. grandfather prostate 70s	Y
					PMS2	c.1281delT	p.H428Tfs*20		Y
426565	Female	30		Deficient	*MSH2*	c.2388delT	p.V797Lfs*15	Father colon 60; Pat. half-sister 1 endometrial 54; Pat. half-sister 2 thyroid 39; Pat. aunt melanoma 60s; Mat. aunt breast 47; Mat. grandmother brain 52	Y
					MUTYH	c.1187G>A	p.G396D		N[d]
429807	Female	32	Polyposis. Synchronous thyroid cancer.	Proficient	*APC*	c.1759delA	p.S587Afs*3	Father colon 52, small bowel 55, FAP; Mother colon 50, Pat. aunt colon 43	Y
440605	Male	32	Attenuated polyposis.	Proficient	*MUTYH*	c.536A>G	p.Y179C	Brother polyps; Mother skin 60s	Y
					MUTYH	c.536A>G	p.Y179C		
406486	Male	32	Synchronous primaries. Ashkenazi Jewish ancestry denied.	Proficient	*APC*	c.3920T>A	p.I1307K	Mother cervical 35; Mat. grandmother colon 65; Pat. grandmother breast 40s	N[d]
366716	Male	33		Deficient	*MLH1*	c.200G>A	p.G67E	Father colon 41; Pat. aunt	Y

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Patient #	**Sex**	**Age**	**Clinical history**	**MMR tumor status[f]**	**Gene**	**Nucleotide change**	**Protein change**	**Family history[b]**	**Met NCCN criteria[g]**
								bladder 55; Pat. grandmother pancreatic 50s	
444839	Female	33	Polyposis.	Proficient	*APC*	c.3747C>A	p.C1249X	None	Y
364392	Female	34		Deficient	*MLH1*	c.1279C>T	p.Q427X	Father[a] epocrine 33; Sister[a] endometrial 36, ovarian 36; Pat. uncle brain 60s, Pat. aunt breast age unknown	Y
500685	Male	34		Deficient	*MLH1*	c.1381A>T	p.K461X	Mother hepatocellular 52	Y
459709	Female	34		Deficient	*MLH1*	Constitutional methylation		None[c]	Y
364390	Male	35		Deficient	*MSH2*	c.1885C>T	p.Q629X	Father colon 56; Pat. aunt colon 50s, endometrial 50s; Pat. grandmother "abdominal cancer" 30s; Mother lung 55	Y
444774	Female	35	Polyposis.	Proficient	*APC*	c.4583_4587del	p.V1528Gfs*3	Mother FAP	Y
440927	Female	35		Proficient	*MUTYH*	c.1187G>A	p.G396D	Father lung 67, esophageal 67[c]	N[d]
453021	Male	36		Proficient	*ATM*	c.170G>A	p.W57X	None	N[e]
410275	Female	36		Proficient	*ATM*	exon 8 deletion		Pat. half-sister "female cancer" 41; Pat. aunt 1 brain 40s; Pat. aunt 2 breast 60s; Pat. grandmother breast 50s; Mat. aunt brain 50s	N[e]
365403	Male	37		Deficient	*PMS2*	c.1831dup	p.I611Nfs*2	Mother breast 61; Mat. grandfather prostate 60s	Y
430190	Male	37		Deficient	*MSH2*	c.1832T>A	p.V611E	Mother stomach 60s; Mat. half-brother cancer site unknown 48; Pat. grandfather colon 70s	Y
369727	Female	38		Deficient	*MSH2*	exon 8 deletion		Mother[a] endometrial 60, colon 62; Mat. aunt colon 50; Mat. grandfather colon 20s	Y
418007	Male	38		Proficient	*MUTYH*	c.1280_1289del	p.W427Sfs*22	Mother lymphoma 51	N[d]
398885	Male	38		Proficient	*MUTYH*	c.536A>G	p.Y179C	Father lung 50[c]	N[d]
362938	Male	39	4 adenomas, multiple	Deficient	*MUTYH*	c.1187G>A	p.G396D	Father skin 74; Brother adenomas 20s; Mat. uncle	N
					MUTYH	c.698G>A	p.G233D		

eTable 3. Genotypes and Phenotypes of Patients with a Hereditary Cancer Syndrome									
Patient #	**Sex**	**Age**	**Clinical history**	**MMR tumor status[f]**	**Gene**	**Nucleotide change**	**Protein change**	**Family history[b]**	**Met NCCN criteria[g]**
			hyperplastic rectal polyps.					colon 63	
248119	Male	39	No polyps.	Proficient	*SMAD4*	c.430_431del	p.S144Rfs*7	Sister mixed polyposis 35 (adenomas, hyperplastic); Mother gastric polyposis; Mat. grandmother breast 42	N
375800	Male	40		Proficient	*ATM*	c.8395_8404del	p.F2799Kfs*4	Father esophageal 26; Pat. uncle polyps 60s; Pat. grandfather colon 70; Pat. grandmother colon 51	N[e]
434386	Female	41	Ashkenazi Jewish ancestry denied.	Proficient	*APC*	c.3920T>A	p.I1307K	Mat. uncle cancer site/age unknown; Pat. uncle pancreatic age unknown; Pat. aunt ovarian age unknown	N[d]
426810	Male	41	Ashkenazi Jewish ancestry denied.	Deficient[g]	*APC*	c.3920T>A	p.I1307K	Mat. grandfather prostate age unknown	N[d]
417173	Male	41	Known mutation in family.	Deficient	*MSH2*	exon 1-6 deletion		Mother[a] colon 43, 49; Mat. aunt ovarian 50s; Mat. uncle colon 41	Y
365417	Male	41		Proficient	*BRCA2*	c.961C>T	p.Q321X	Father colon 68; Sister polyps 40s; Mat. uncle ureter 65, Mat. grandmother melanoma 55, pancreatic 56	N
362943	Female	42		Proficient	*MUTYH*	c.1187G>A	p.G396D	None[c]	N[d]
362982	Male	42	Synchronous primaries. Known mutation in family.	Deficient	*MLH1*	c.117-2A>G		Father[a] colon 50s, 64; Pat. half-brother 1 colon 20s, 42; Pat. half-brother 2 colon 50s; Pat. half-sister "female cancer" 50s; Pat. grandmother colon age unknown	Y
410711	Male	42	Synchronous primaries.	Deficient	*MSH2*	c.1386+1G>T		Mother endometrial 36; Sister endometrial 36	Y
445718	Male	42		Deficient	*MSH6*	c.1109 T>C	p.L370S	Father[a] appendiceal 38, prostate 45; Pat. grandmother[a]	Y

eTable 3. Genotypes and Phenotypes of Patients with a Hereditary Cancer Syndrome									
Patient #	**Sex**	**Age**	**Clinical history**	**MMR tumor status[f]**	**Gene**	**Nucleotide change**	**Protein change**	**Family history[b]**	**Met NCCN criteria[g]**
								endometrial 75; Mother endometrial 52; Mat. grandmother breast 52	
367288	Female	42		Deficient	*MSH6*	c.3438+1G>A		None	Y
430485	Male	42		Deficient	*PMS2*	c.1831dup	p.I611Nfs*2	Mother "female cancer" 40s; Mat. aunt cancer site unknown 60; Mat. cousin brain 47	Y
445023	Female	42	Ashkenazi Jewish ancestry denied.	Proficient	*BRCA1*	c.5266dupC	p.Q1756Pfs*74	Father[a] polyps 50s; Mother polyps; Pat. grandmother breast 60, ovarian 60	Y
452726	Female	43		Deficient	*MSH2*	exon 1-6 deletion		Mother colon 59; Sister endometrial age unknown[a]; Mat. grandmother colon age unknown	Y
432388	Female	44	Synchronous primaries.	Deficient	*MLH1*	c.207+1G>A		Mother colon 42, biliary tract 52, cervical 60; Sister colon 35	Y
417591	Male	44		Deficient	*MLH1*	c.589-2A>G		Mother thyroid age unknown, polyps; Mat. grandmother colon 30s	Y
432587	Female	44		Deficient	*MSH2*	c.2131C>T	p.R711X	Unknown, adopted	Y
423450	Male	44		Deficient	*PMS2*	c.2113G>A	p.E705K	Father melanom[a] 77; Pat. uncle leukemia 50s; Pat. grandmother colon 70s	Y
442703	Female	44		Proficient	*ATM*	c.7271T>G	p.V2424G	Father prostate 74; Mother breast 50s; Mat. grandmother breast 50s	N[e]
					CHEK2	c.1100del	p.T367Mfs*15		N[e]
419748	Female	44		Proficient	*BRCA2*	c.7069_7070del	p.L2357Vfs*2	Pat. grandmother cancer site/age unknown; Mat. uncle melanoma age unknown	N
457664	Female	44	Known mutation in the family.	Deficient	*PMS2*	c.1874delT	p.L625X	Pat. uncle colon 68; Pat. grandfather[a] colon 85	Y
448585	Female	44		Proficient	*MUTYH*	c.1187G>A	p.G396D	Father lung 81; Sister breast 52; Mat. grandmother pancreatic 84; Pat.	N[d]

eTable 3. Genotypes and Phenotypes of Patients with a Hereditary Cancer Syndrome									
Patient #	**Sex**	**Age**	**Clinical history**	**MMR tumor status[f]**	**Gene**	**Nucleotide change**	**Protein change**	**Family history[b]**	**Met NCCN criteria[g]**
								grandfather lung age unknown; Pat. uncle lung age unknown	
362978	Male	45		Proficient	*CDKN2A*	c.9_32dup	p.A4_P11dup	Mother melanoma 60s, 2-3 dysplastic moles, 5 adenomas; Mat. grandmother colon 70s; Pat. uncle colon 50s	N
440170	Male	45		Proficient	*MUTYH*	c.1187G>A	p.G396D	Sister breast 39[c]	N[d]
369732	Female	45		Proficient	*PALB2*	exon 11 deletion		Father brain 69; Pat. aunt leukemia 70s	N[e]
455447	Male	45	Ashkenazi Jewish ancestry denied.	Proficient	*APC*	c.3920T>A	p.I1307K	Mother breast 69, pancreatic 69; Mat. grandmother breast 55; Mat. grandfather lymphoma 30s; Pat. grandmother colon 80; Pat. grandfather prostate 60s; Pat. uncle bone 63; Pat. aunt colon 60s, lung 72	N[d]
364370	Female	46	Metachronous colon cancer 28.	Deficient	*MLH1*	c.2252_2253delAA	p.K751Sfs*3	Father colon 40; Pat. grandmother colon 29	Y
455899	Female	46	Metachronous breast cancer 45.	Proficient	*PALB2*	c.758dupT	p.S254Ifs*3	Father lymphoma 51; Pat. aunt 1 breast 74; Pat. aunt 2 breast 65; Mat. aunt melanoma 60s; Mat. grandmother breast 60	N[e]
362955	Male	47		Deficient	*MSH2*	exon 1-6 deletion		Father[a] prostate 50s, colon 63; Pat. half-sister colon 60s; Pat. half-brother colon 60s; Pat. uncle colon 45; Pat. aunt 1 brain 56; Pat. aunt 2 ureter 50s, kidney 60s; Pat. grandfather colon 46	Y
405351	Female	47		Deficient	*MSH2*	exon 3-6 deletion		Mother leukemia 30s; Sister colon 50	Y
404793	Female	47		Proficient	*BRCA1*	c.181T>G	p.C61G	Father prostate 70s; Mother	Y

eTable 3. Genotypes and Phenotypes of Patients with a Hereditary Cancer Syndrome									
Patient #	**Sex**	**Age**	**Clinical history**	**MMR tumor status[f]**	**Gene**	**Nucleotide change**	**Protein change**	**Family history[b]**	**Met NCCN criteria[g]**
								breast 49, ovarian 56; Mat. aunt breast 42	
448307	Female	47		Proficient	*BRCA2*	c.1755_1759del	p.K585Nfs*3	Mat. half-sister skin 38; Father esophageal 40s; Mat. aunt 1 breast 60s; Mat. aunt 2 breast and ovarian age unknown; Mat. uncle colon 53; Mat. grandmother carcinomatosis 62; Pat. grandmother pancreatic age unknown	Y
458192	Female	47	Synchronous primaries; *MLH1* methylation absent. Metachronous endometrial cancer 49; *MLH1* methylation present.	Deficient	*MLH1*	c.1635dup	p.K546Qfs*11	Mother bilateral breast 54	Y
454646	Female	47		Deficient	*MLH1*	c.2041G>A	p.A681T	None	Y
195126	Male	48	Sebaceous gland cancer 45. Known mutation in family.	Deficient	*MLH1*	c.1210_1211del	p.L404Vfs*12	Father[a] colon 60; Sister rhabdomyosarcoma 27; Brother 1 colon 32, prostate 56; Brother 2 colon 60; Pat. uncle gastric; Pat. grandmother and grandfather colon age unknown	Y
443516	Male	48	Metachronous colon cancer 34.	Deficient	*MLH1*	c.1667+1G>A		Father colon 34; Sister gallbladder 41	Y
408570	Female	48		Deficient	*MLH1*	c.207+5G>C		Mother breast 74; Father[a] colon 31, 53, GE junction 73; Brother[a] colon 48; Sister adrenal 39, thyroid 39; Pat.	Y

eTable 3. Genotypes and Phenotypes of Patients with a Hereditary Cancer Syndrome									
Patient #	**Sex**	**Age**	**Clinical history**	**MMR tumor status[f]**	**Gene**	**Nucleotide change**	**Protein change**	**Family history[b]**	**Met NCCN criteria[g]**
								grandmother colon 37	
4274	Female	48	Metachronous gastric cancer 48. Known mutation in family.	Deficient	*MSH2*	c.1477C>T	p.Q493X	Father[a] pancreatic 50; Brother bile duct 37, colon 43; Pat. aunt 1 breast 58; Pat. aunt 2 colon 38; Pat. aunt 3[a] colon 46, 60, gallbladder 68; Pat. grandmother colon 70	Y
366413	Male	48	Synchronous primaries (3).	Deficient	*MSH2*	c.2096C>A	p.S699X	Mother endometrial 34, colon 45, kidney 62; Father colon 68; Mat. aunt leukemia 65; Pat. uncle colon 50s; Pat. grandmother endometrial 50s	Y
404530	Male	48	Known mutation in family.	Deficient	*MSH2*	c.942+3A>T		Mother[a] colon 44, bladder 60; Mat. grandmother breast 71, endometrial 71	Y
362971	Male	48	Known mutation in family. Ashkenazi Jewish ancestry.	Proficient	*BRCA2*	c.5946del	p.S1982Rfs*22	Mother breast 48; Brother polyps 40s; Mat. uncle colon 50s; 2 Mat. aunts ovarian; Mat. grandfather pancreatic 78	Y
440679	Male	48		Proficient	*MUTYH*	c.1187G>A	p.G396D	None[c]	N[d]
423526	Female	49		Deficient	*MSH2*	exon 13-14 deletion		None	Y
443029	Male	49		Deficient	*MSH2*	exon 3-16 deletion		Mother[a] colon 35; Brother 1 colon 51; Brother 2 colon 39	Y
366298	Male	49	Polyposis. Synchronous bilateral renal cell cancers.	Deficient	*MUTYH* *MUTYH*	c.536A>G c.1187G>A	p.Y179C p.G396D	None	Y
423828	Male	49		Deficient	*PMS2*	c.215G>A	p.G72E	Father[a] colon 58	Y
363017	Female	49	Attenuated polyposis.	Proficient	*APC*	c.1213C>T	p.R405X	None	Y
410867	Female	49	4 adenomas.	Proficient	*MUTYH* *MUTYH*	c.536A>G c.1187G>A	p.Y179C p.G396D	Brother colon 42 (MMR proficient, non-polyposis); Father colon 59; Pat.	N

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Patient #	**Sex**	**Age**	**Clinical history**	**MMR tumor status[f]**	**Gene**	**Nucleotide change**	**Protein change**	**Family history[b]**	**Met NCCN criteria[g]**
								grandfather colon age unknown	

Abbreviations: MMR, mismatch repair; NCCN, National Comprehensive Cancer Network; Mat, Maternal; Pat, Paternal
[a]Indicates mutation carrier, when known
[b]First- and second-degree relatives
[c]Second-degree relative cancer history unavailable
[d]NCCN testing criteria nonexistent for monoallelic *MUTYH* or *APC* p.I1307K, patient did not meet NCCN testing criteria for *APC* or *MUTYH* (polyposis)
[e]NCCN testing criteria nonexistent, patient did not meet NCCN testing criteria for *BRCA1/2*
[f]MMR deficient tumor = microsatellite instability and/or abnormal immunohistochemistry, MMR proficient tumor = microsatellite stability and/or normal immunohistochemistry
[g]For the gene in which they were found to have a mutation

eTable 4. Patients Explained by Double Somatic Mutations									
Patient #	**Sex**	**Age**	**MSI**	**MLH1-hm**	**IHC**	**Germline pathogenic mutation(s)**	**MMR somatic tumor testing**	**Family cancer history (FDRs)**	**Conclusion**
362933	Female	37	MSI-H	Absent	Absent MLH1/PMS2	None	*MLH1* c.790+5 G>A plus LOH	Mother pancreatic neuroendocrine 58	Double somatic
363002	Male	41	MSI-H	Absent	Absent MLH1/PMS2	None	*MLH1* c.178C>T, p.Q60X plus LOH	Mother breast 56	Double somatic
426745	Male	45	MSI-H	Absent	Absent MLH1/PMS2	None	*MLH1* c.439G>A, p.G147R plus LOH	Mother colon 67, melanoma 67	Double somatic
366535	Male	40	MSI-H	Absent	Absent PMS2 only	None	*MLH1* c.2248_2253dup, p.Y750_K751dup plus LOH	None	Double somatic
426966	Male	46	MSI-H	Absent	Weak MSH2/absent MSH6	None	*MSH6* c.718C>T, p.R240X *MSH6* c.3261dupC, p.F1088Lfs*5	Mother colon 72	Double somatic
448651	Male	40	MSI-H	Absent	Absent MSH2/weak MSH6	None	*MSH2* c.1865C>T, p.P622L *MSH2* c.1662-2A>G	None	Double somatic
400308	Female	40	MSI-H	Absent	Absent MLH1/PMS2	None	*MLH1*[a] c.1646T>C, p.L549P *MLH1*[a] c.562G>A, p.A188T	Sister skin 39	Likely double somatic
362938	Male	39	MSI-H	Absent	Weak MLH1/absent PMS2	*MUTYH* c.1187G>A, p.G396D *MUTYH* c.698G>A, p.G233D	*MLH1* c.2135G>A, p.W712X *MLH1* c.2041G>A, p.A681T	Father skin 74; Brother adenomas 20s; Maternal uncle colon 63	Double somatic and *MUTYH*-associated polyposis
366298	Male	49	MSI-H	Absent	Absent	*MUTYH*	*MLH1* c.677G>A,	None	Double

eTable 4. Patients Explained by Double Somatic Mutations									
Patient #	**Sex**	**Age**	**MSI**	**MLH1-hm**	**IHC**	**Germline pathogenic mutation(s)**	**MMR somatic tumor testing**	**Family cancer history (FDRs)**	**Conclusion**
					MLH1/PMS2	c.536A>G, p.Y179C *MUTYH* c.1187G>A, p.G396D	p.R226Q plus LOH		somatic and *MUTYH*-associated polyposis

Abbreviations: MMR, mismatch repair; MSI-H, high microsatellite instability; MSS, microsatellite stability; hm, hypermethylation; IHC, immunohistochemistry; LOH, loss of heterozygosity; FDR, first-degree relative

[a]Variant of uncertain significance