Supplementary Table 1: Complete list of genes sequenced

Gene	N. of patients tested	%
APC	70	100
MUTYH (full seq.)	53	75.7
MLH1	43	61.4
MSH2	43	61.4
MSH6	42	60.0
PMS2	42	60.0
EPCAM	41	58.5
CHEK2	39	55.7
TP53	39	55.7
BMPR1A	38	54.2
CDH1	38	54.2
PTEN	38	54.2
SMAD4	38	54.2
STK11	38	54.2
GREM1	36	51.4
POLD1	36	51.4
POLE	36	51.4
ATM	33	47.1
AXIN2	28	40.0
BRCA1	23	32.8
BRCA2	23	32.8
NBN	21	30.0
PALB2	21	30.0
RAD51D	21	30.0
BARD1	19	27.1
CDKN2A	19	27.1
RAD51C	19	27.1
BRIP1	18	25.7

NF1	17	24.2
MUTYH (Y179C and G396D mutations only)	17	24.2
CDK4	16	22.8
SMARCA4	16	22.8
NTHL1	15	21.4
RAD50	15	21.4
DICER1	14	20.0
HOXB13	14	20.0
MSH3	13	18.5
VHL	13	18.5
MEN1	12	17.1
SDHA	12	17.1
SDHB	12	17.1
SDHC	12	17.1
SDHD	12	17.1
TSC1	12	17.1
TSC2	12	17.1
KIT	10	14.2
FLCN	9	12.8
PDGFRA	9	12.8
CTNNA1	8	11.4
BAP1	7	10.0
BLM	7	10.0
FH	7	10.0
MAX	7	10.0
MITF	7	10.0
RET	7	10.0
SDHAF2	7	10.0

TMEM127	7	10.0
MRE11A	7	10.0
GALNT12	7	10.0
ALK	6	8.5
CDC73	6	8.5
MET	6	8.5
NF2	6	8.5
PHOX2B	6	8.5
PRKAR1A	6	8.5
PTCH1	6	8.5
RB1	6	8.5
SMARCB1	6	8.5
SUFU	6	8.5
AIP	5	7.1
CDKN1B	5	7.1
EGFR	5	7.1
POT1	5	7.1
RECQL4	5	7.1
SMARCE1	5	7.1
FANCC	5	7.1
TERT	4	5.7
RPS20	4	5.7
CASR	3	4.2
WT1	3	4.2
MLH3	3	4.2
CDKN1C	2	2.8
CEBPA	2	2.8
DIS3L2	2	2.8
GATA2	2	2.8
GPC3	2	2.8

HRAS	2	2.8
RUNX1	2	2.8
TERC	2	2.8
WRN	2	2.8
XRCC2	2	2.8
KIF1B	2	2.8
LZTR1	2	2.8
EGLN1	2	2.8
FAM175A	2	2.8
PALLD	2	2.8
RINT1	2	2.8
BUB1B	2	2.8
ENG	2	2.8
XRCC2	2	2.8
CTRC	1	1.4
FANCA	1	1.4
RNF43	1	1.4
CFTR	1	1.4
CPA1	1	1.4
PRSS1	1	1.4
SPINK1	1	1.4
CEP57	1	1.4

Supplementary Table 2. Adenomatous polyp histology in patients with CPUE

Histology	Total adenomas (N=348)	%
Tubular adenoma- low-grade dysplasia	313	89.9
Tubular adenoma- high-grade dysplasia	7	2.0
Tubulovillous adenoma- low-grade dysplasia	23	6.6
Tubulovillous adenoma- high-grade dysplasia	4	1.1
Villous adenoma- low-grade dysplasia	1	0.3

Supplementary Table 2. Adenomatous polyp histology type distribution calculated from 348 colonoscopy reports, excluding cases in which intramucosal carcinoma or colorectal cancer were diagnosed.

Supplementary Table 3. Clinical correlations for patients with a significant clinical outcome (Intramucosal cancer, invasive cancer, or colectomy)

Clinical characteristics	Significant clinical outcome group (N=11)	Patients without cancer or colectomy (N=59)	[a]P-value
Males	7 (63.6%)	41 (69.5%)	0.73
Smokers	6 (54.5%)	35 (60.3%)	0.74
Metabolic comorbidities	3 (27.3%)	26 (44.1%)	0.34
Presence of FDR with malignancy	7 (63.6%)	46 (78.0%)	0.44
Presence of FDR with CRC	(27.3%) 17	17 (28.8%)	1
Cumulative adenoma burden (Mean rank)	42.91	34.12	[b] 0.18
Number of FDR with any malignancy (Mean rank)	29.68	36.58	[b] 0.27
Number of FDR with CRC (Mean rank)	35.69	34.50	[b] 0.82

Number of colonoscopies (Mean rank)	34.82	35.63	[b] 0.80
Number of different extra colonic malignancy (Mean rank)	35.09	35.58	[b] 0.93
Colonoscopy surveillance period (months) (Mean+-SD)	140.1250+-87.10	148.3818+-73.44	[c] 0.80

Supplementary Table 3. Comparison between the patients with significant outcome (N=11) to the rest of the cohort (N=59). No significant difference in any of the parameters examined was found. [a] Fisher's Exact Test - Exact, [b] Mann-Whitney U test. [c] 2-sided t-test for Equality of Means Significance

Supplementary Table 4. Extra colonic malignancies and potential clinical predictors-Univariable logistic regression.

	Odds ratio (OR)	95% C.I. for OR		P value
		Lower	Upper	
Any ECM (N=35)				
Cumulative adenoma burden	0.998	0.973	1.024	0.885
Gender	1.000	0.364	2.744	1.000
Breast cancer (N=4)				
Cumulative adenoma burden	1.016	0.972	1.063	0.483
Age	0.889	0.811	0.976	**0.013**
Prostate cancer (N=6)				
Cumulative adenoma burden	0.976	0.915	1.042	0.471
Age	0.957	0.884	1.036	0.281
Melanoma (N=5)				
Cumulative adenoma burden	0.995	0.943	1.050	0.858
Age	0.906	0.840	0.977	**0.010**
Gender	0.667	0.103	4.304	0.670
Non-melanoma skin cancer (N=25)				
Cumulative adenoma burden	1.006	0.979	1.034	0.655
Age	0.951	0.903	1.002	0.057
Gender	1.865	0.585	5.944	0.292

Supplementary Table 4. Univariable logistic regression analysis was used to estimate the relationship between categorical dependent variables (extra colonic malignancies) and different independent variables and their prediction potential.