Supplementary Table 1. Genes included in FoundationOne assay

ABL1	*BRAF*	*CHEK1*	*FANCC*	*GATA3*	*JAK2*	*MITF*	*PDCD1LG2*	*RBM10*	*STAT4*
ABL2	*BRCA1*	*CHEK2*	*FANCD2*	*GATA4*	*JAK3*	*MLH1*	*PDGFRA*	*RET*	*STK11*
ACVR1B	*BRCA2*	*CIC*	*FANCE*	*GATA6*	*JUN*	*MPL*	*PDGFRB*	*RICTOR*	*SUFU*
AKT1	*BRD4*	*CREBBP*	*FANCF*	*GID4 (C17orf39)*	*KAT6A (MYST3)*	*MRE11A*	*PDK1*	*RNF43*	*SYK*
AKT2	*BRIP1*	*CRKL*	*FANCG*	*GLI1*	*KDM5A*	*MSH2*	*PIK3C2B*	*ROS1*	*TAF1*
AKT3	*BTG1*	*CRLF2*	*FANCL*	*GNA11*	*KDM5C*	*MSH6*	*PIK3CA*	*RPTOR*	*TBX3*
ALK	*BTK*	*CSF1R*	*FAS*	*GNA13*	*KDM6A*	*MTOR*	*PIK3CB*	*RUNX1*	*TERC*
AMER1 (FAM123B)	*C11orf30 (EMSY)*	*CTCF*	*FAT1*	*GNAQ*	*KDR*	*MUTYH*	*PIK3CG*	*RUNX1T1*	*TERT (promoter only)*
APC	*CARD11*	*CTNNA1*	*FBXW7*	*GNAS*	*KEAP1*	*MYC*	*PIK3R1*	*SDHA*	*TET2*
AR	*CBFB*	*CTNNB1*	*FGF10*	*GPR124*	*KEL*	*MYCL (MYCL1)*	*PIK3R2*	*SDHB*	*TGFBR2*
ARAF	*CBL*	*CUL3*	*FGF14*	*GRIN2A*	*KIT*	*MYCN*	*PLCG2*	*SDHC*	*TNFAIP3*
ARFRP1	*CCND1*	*CYLD*	*FGF19*	*GRM3*	*KLHL6*	*MYD88*	*PMS2*	*SDHD*	*TNFRSF14*
ARID1A	*CCND2*	*DAXX*	*FGF23*	*GSK3B*	*KMT2A (MLL)*	*NF1*	*POLD1*	*SETD2*	*TOP1*
ARID1B	*CCND3*	*DDR2*	*FGF3*	*H3F3A*	*KMT2C (MLL3)*	*NF2*	*POLE*	*SF3B1*	*TOP2A*
ARID2	*CCNE1*	*DICER1*	*FGF4*	*HGF*	*KMT2D (MLL2)*	*NFE2L2*	*PPP2R1A*	*SLIT2*	*TP53*
ASXL1	*CD274*	*DNMT3A*	*FGF6*	*HNF1A*	*KRAS*	*NFKBIA*	*PRDM1*	*SMAD2*	*TSC1*
ATM	*CD79A*	*DOT1L*	*FGFR1*	*HRAS*	*LMO1*	*NKX2-1*	*PREX2*	*SMAD3*	*TSC2*
ATR	*CD79B*	*EGFR*	*FGFR2*	*HSD3B1*	*LRP1B*	*NOTCH1*	*PRKAR1A*	*SMAD4*	*TSHR*
ATRX	*CDC73*	*EP300*	*FGFR3*	*HSP90AA1*	*LYN*	*NOTCH2*	*PRKCI*	*SMARCA4*	*U2AF1*
AURKA	*CDH1*	*EPHA3*	*FGFR4*	*IDH1*	*LZTR1*	*NOTCH3*	*PRKDC*	*SMARCB1*	*VEGFA*
AURKB	*CDK12*	*EPHA5*	*FH*	*IDH2*	*MAGI2*	*NPM1*	*PRSS8*	*SMO*	*VHL*
AXIN1	*CDK4*	*EPHA7*	*FLCN*	*IGF1R*	*MAP2K1*	*NRAS*	*PTCH1*	*SNCAIP*	*WISP3*
AXL	*CDK6*	*EPHB1*	*FLT1*	*IGF2*	*MAP2K2*	*NSD1*	*PTEN*	*SOCS1*	*WT1*
BAP1	*CDK8*	*ERBB2*	*FLT3*	*IKBKE*	*MAP2K4*	*NTRK1*	*PTPN11*	*SOX10*	*XPO1*
BARD1	*CDKN1A*	*ERBB3*	*FLT4*	*IKZF1*	*MAP3K1*	*NTRK2*	*QKI*	*SOX2*	*ZBTB2*
BCL2	*CDKN1B*	*ERBB4*	*FOXL2*	*IL7R*	*MCL1*	*NTRK3*	*RAC1*	*SOX9*	*ZNF217*
BCL2L1	*CDKN2A*	*ERG*	*FOXP1*	*INHBA*	*MDM2*	*NUP93*	*RAD50*	*SPEN*	*ZNF703*
BCL2L2	*CDKN2B*	*ERRFI1*	*FRS2*	*INPP4B*	*MDM4*	*PAK3*	*RAD51*	*SPOP*	
BCL6	*CDKN2C*	*ESR1*	*FUBP1*	*IRF2*	*MED12*	*PALB2*	*RAF1*	*SPTA1*	
BCOR	*CEBPA*	*EZH2*	*GABRA6*	*IRF4*	*MEF2B*	*PARK2*	*RANBP2*	*SRC*	
BCORL1	*CHD2*	*FAM46C*	*GATA1*	*IRS2*	*MEN1*	*PAX5*	*RARA*	*STAG2*	
BLM	*CHD4*	*FANCA*	*GATA2*	*JAK1*	*MET*	*PBRM1*	*RB1*	*STAT3*	

Select Rearrangements									
ALK	*BRAF*	*BRD4*	*ETV4*	*FGFR1*	*KIT*	*MYC*	*NTRK2*	*RARA*	*TMPRSS2*
BCL2	*BRCA1*	*EGFR*	*ETV5*	*FGFR2*	*MSH2*	*NOTCH2*	*PDGFRA*	*RET*	
BCR	*BRCA2*	*ETV1*	*ETV6*	*FGFR3*	*MYB*	*NTRK1*	*RAF1*	*ROS1*	

Supplementary Table 2. Genes included in MSK-IMPACT assay

ABL1	*BRCA1*	*CTLA4*	*FAM175A*	*HIST1H3B*	*MAP2K1*	*NFE2L2*	*PLK2*	*RNF43*	*SYK*
AKT1	*BRCA2*	*CTNNB1*	*FAM46C*	*HNF1A*	*MAP2K2*	*NKX2-1*	*PMAIP1*	*ROS1*	*TBX3*
AKT2	*BRD4*	*CUL3*	*FANCA*	*HRAS*	*MAP2K4*	*NKX3-1*	*PMS1*	*RPS6KA4*	*TERT*
AKT3	*BRIP1*	*DAXX*	*FANCC*	*ICOSLG*	*MAP3K1*	*NOTCH1*	*PMS2*	*RPS6KB2*	*TET1*
ALK	*BTK*	*DCUN1D1*	*FAT1*	*IDH1*	*MAP3K13*	*NOTCH2*	*PNRC1*	*RPTOR*	*TET2*
ALOX12B	*CARD11*	*DDR2*	*FBXW7*	*IDH2*	*MAPK1*	*NOTCH3*	*POLE*	*RUNX1*	*TGFBR1*
APC	*CASP8*	*DICER1*	*FGF19*	*IFNGR1*	*MAX*	*NOTCH4*	*PPP2R1A*	*RYBP*	*TGFBR2*
AR	*CBFB*	*DIS3*	*FGF3*	*IGF1*	*MCL1*	*NPM1*	*PRDM1*	*SDHA*	*TMEM127*
ARAF	*CBL*	*DNMT1*	*FGF4*	*IGF1R*	*MDC1*	*NRAS*	*PRKAR1A*	*SDHAF2*	*TMPRSS2*
ARID1A	*CCND1*	*DNMT3A*	*FGFR1*	*IGF2*	*MDM2*	*NSD1*	*PTCH1*	*SDHB*	*TNFAIP3*
ARID1B	*CCND2*	*DNMT3B*	*FGFR2*	*IKBKE*	*MDM4*	*NTRK1*	*PTEN*	*SDHC*	*TNFRSF14*
ARID2	*CCND3*	*DOT1L*	*FGFR3*	*IKZF1*	*MED12*	*NTRK2*	*PTPN11*	*SDHD*	*TOP1*
ARID5B	*CCNE1*	*E2F3*	*FGFR4*	*IL10*	*MEF2B*	*NTRK3*	*PTPRD*	*SETD2*	*TP53*
ASXL1	*CD274*	*EED*	*FH*	*IL7R*	*MEN1*	*PAK1*	*PTPRS*	*SF3B1*	*TP63*
ASXL2	*CD276*	*EGFL7*	*FLCN*	*INPP4A*	*MET*	*PALB2*	*PTPRT*	*SH2D1A*	*TRAF7*
ATM	*CD79B*	*EGFR*	*FLT1*	*INPP4B*	*MITF*	*PARK2*	*RAC1*	*SHQ1*	*TSC1*
ATR	*CDC73*	*EIF1AX*	*FLT3*	*INSR*	*MLH1*	*PARP1*	*RAD50*	*SMAD2*	*TSC2*
ATRX	*CDH1*	*EP300*	*FLT4*	*IRF4*	*MLL*	*PAX5*	*RAD51*	*SMAD3*	*TSHR*
AURKA	*CDK12*	*EPCAM*	*FOXA1*	*IRS1*	*MLL2*	*PAK7*	*RAD51B*	*SMAD4*	*U2AF1*
AURKB	*CDK4*	*EPHA3*	*FOXL2*	*IRS2*	*MLL3*	*PBRM1*	*RAD51C*	*SMARCA4*	*VHL*
AXIN1	*CDK6*	*EPHA5*	*FOXP1*	*JAK1*	*MPL*	*PDCD1*	*RAD51D*	*SMARCB1*	*VTCN1*
AXIN2	*CDK8*	*EPHB1*	*FUBP1*	*JAK2*	*MRE11A*	*PDGFRA*	*RAD52*	*SMARCD1*	*WT1*
AXL	*CDKN1A*	*ERBB2*	*GATA1*	*JAK3*	*MSH2*	*PDGFRB*	*RAD54L*	*SMO*	*XIAP*
B2M	*CDKN1B*	*ERBB3*	*GATA2*	*JUN*	*MSH6*	*PDPK1*	*RAF1*	*SOCS1*	*XPO1*
BAP1	*CDKN2A*	*ERBB4*	*GATA3*	*KDM5A*	*MTOR*	*PHOX2B*	*RARA*	*SOX17*	*YAP1*
BARD1	*CDKN2B*	*ERCC2*	*GNA11*	*KDM5C*	*MUTYH*	*PIK3C2G*	*RASA1*	*SOX2*	*YES1*
BBC3	*CDKN2C*	*ERCC3*	*GNAQ*	*KDM6A*	*MYC*	*PIK3C3*	*RB1*	*SOX9*	
BCL2	*CHEK1*	*ERCC4*	*GNAS*	*KDR*	*MYCL1*	*PIK3CA*	*RBM10*	*SPEN*	
BCL2L1	*CHEK2*	*ERCC5*	*GREM1*	*KEAP1*	*MYCN*	*PIK3CB*	*RECQL4*	*SPOP*	
BCL2L11	*CIC*	*ERG*	*GRIN2A*	*KIT*	*MYD88*	*PIK3CD*	*REL*	*SRC*	
BCL6	*CREBBP*	*ESR1*	*GSK3B*	*KLF4*	*MYOD1*	*PIK3CG*	*RET*	*STAG2*	
BCOR	*CRKL*	*ETV1*	*H3F3C*	*KRAS*	*NBN*	*PIK3R1*	*RFWD2*	*STK11*	
BLM	*CRLF2*	*ETV6*	*HGF*	*LATS1*	*NCOR1*	*PIK3R2*	*RHOA*	*STK40*	
BMPR1A	*CSF1R*	*EZH2*	*HIST1H1C*	*LATS2*	*NF1*	*PIK3R3*	*RICTOR*	*SUFU*	
BRAF	*CTCF*	*FAM123B*	*HIST1H2BD*	*LMO1*	*NF2*	*PIM1*	*RIT1*	*SUZ12*	

Supplementary Table 3. Spectrum of *TP53* alterations

Patient number	TP53 alteration	Putative functional consequence	Duration of IBD	Stage of disease
CROHN'S DISEASE ASSOCIATED CASES				
1	R248W	GOF	>10 years	2
2	P278S	GOF	>10 years	4
3	D281E	unknown	>10 years	2
4	R248Q	GOF	>10 years	1
5	W146*	LOF	>10 years	4
6	R213*	LOF	>10 years	3
7	R282W	GOF	>10 years	4
8	H193L	unknown	>10 years	4
9	P152L	unknown	>10 years	1
10	C176F	GOF	>10 years	2
11	R248Q	GOF	>10 years	2
12	R282W	GOF	<10 years	4
13	V173L	GOF	<10 years	4
14	P142L	unknown	>10 years	1
15	Splice site 258+1G>A	unknown	>10 years	2
16	R248W, A69V	GOF, unknown	<10 years	2
17	Y234C	unknown	>10 years	3
18	wild-type		<10 years	3
ULCERATIVE COLITIS ASSOCIATED CASES				
19	G199V	unknown	>10 years	1
20	R248Q	GOF	<10 years	3
21	R248Q	GOF	>10 years	1
22	C229fs*	LOF	10 years	1
23	S241F	unknown	>10 years	3
24	L130fs*, V73fs*	LOF, LOF	>10 years	1
25	A161S, M160I	unknown, unknown	>10 years	4
26	R175H	GOF	>10 years	3
27	R342*, R248W	LOF, GOF	<10 years	2
28	G244D	unknown	>10 years	2

29	Splice site 783-1G>A	unknown	>10 years	1
30	L35fs	LOF	>10 years	3
31	R282W	GOF	>10 years	1
32	V172F	unknown	<10 years	1
33	Y126H	unknown	>10 years	2
34	R342*	LOF	>10 years	3
35	R273H	GOF	>10 years	1
36	R213*	LOF	>10 years	3
37	E285K	unknown	>10 years	3
38	Y220C	unknown	>10 years	4
39	Splice site 993+1G>T	unknown	>10 years	3
40	R196*	LOF	<10 years	4
41	M246V	unknown	>10 years	2
42	R248Q	GOF	>10 years	0
43	P190del	LOF	>10 years	1
44	wild-type		<10 years	3
45	wild-type		>10 years	1
46	wild-type		<10 years	3
47	wild-type		>10 years	1

*GOF – gain-of-function, LOF – loss-of-function
Case numbers match order of cases in the oncoprint in Figure 1.

Supplementary Table 4. Clinical characteristics of patients whose tumors were studied. The Table also includes genomic alterations in *APC, MYC,* and *IDH1.*

Patient number	**IBD**	**Duration of IBD**	**Stage at diagnosis**	**Site of primary tumor**	**Special histology**	***APC* status**	***MYC* status**	***IDH1* status**
1	CD	>10 years	2	R colon		MUT		WT
2	CD	>10 years	4	L colon		MUT	AMP	WT
3	CD	>10 years	2	R colon		MUT		MUT
4	CD	>10 years	1	Rectum		MUT		WT
5	CD	>10 years	4	R colon		MUT		WT
6	CD	>10 years	3	Rectum	signet ring	MUT		WT
7	CD	>10 years	4	L colon		WT	AMP	WT
8	CD	>10 years	4	Ileum		WT		WT
9	CD	>10 years	1	Rectum		WT		WT
10	CD	>10 years	2	R colon		WT		WT
11	CD	>10 years	2	R colon		WT	AMP	MUT
12	CD	<10 years	4	R colon		WT	AMP	MUT
13	CD	<10 years	4	Ileum	signet ring	WT		MUT
14	CD	>10 years	1	L colon		WT		MUT
15	CD	>10 years	2	Rectum		WT		WT
16	CD	<10 years	2	R colon		WT		WT
17	CD	>10 years	3	Rectum		WT		WT
18	CD	<10 years	3	L colon		MUT	AMP	WT
19	UC	>10 years	1	Rectum		MUT	AMP	WT
20	UC	<10 years	3	R colon	signet ring	WT	AMP	WT
21	UC	>10 years	1	L colon		WT	AMP	WT
22	UC	10 years	1	Rectosigmoid		WT	AMP	WT
23	UC	>10 years	3	R colon		WT		WT
24	UC	>10 years	1	Rectum		WT		WT
25	UC	>10 years	4	Rectum		WT		WT
26	UC	>10 years	3	L colon	mucinous	WT		WT
27	UC	<10 years	2	R colon	mucinous	WT		WT
28	UC	>10 years	2	R colon		WT		WT
29	UC	>10 years	1	R colon		WT		WT
30	UC	>10 years	3	Rectum		WT	AMP	WT
31	UC	>10 years	1	Rectosigmoid	signet ring	WT	AMP	WT
32	UC	<10 years	1	Rectosigmoid		WT	AMP	WT
33	UC	>10 years	2	Rectum	mucinous	WT		WT
34	UC	>10 years	3	Rectum		WT		WT
35	UC	>10 years	1	Rectosigmoid		WT		WT
36	UC	>10 years	3	Rectosigmoid		WT		WT
37	UC	>10 years	3	R colon		WT		WT

38	UC	>10 years	4	Rectosigmoid	signet ring	WT	WT
39	UC	>10 years	3	Rectum	mucinous	WT	WT
40	UC	<10 years	4	R colon		WT	WT
41	UC	>10 years	2	Rectosigmoid		WT	WT
42	UC	>10 years	0	Rectosigmoid	signet ring	WT	WT
43	UC	>10 years	1	R colon		WT	WT
44	UC	<10 years	3	R colon	mucinous	MUT	WT
45	UC	>10 years	1	Rectum		MUT	WT
46	UC	<10 years	3	R colon		WT	WT
47	UC	>10 years	1	R colon		WT	WT

CD- Crohn's Disease; UC - Ulcerative colitis; R Colon- right-sided colon; L colon- left-side colon; - mutated gene; WT - wild-type gene; AMP – amplified gene. Special Histology indicates cases in which special histologic features within a well, moderately, or poorly differentiated adenocarcinoma was found on pathologic review. Neither *APC* mutations nor *MYC* amplification status were associated with the clinical features of duration of IBD prior to the diagnosis ofCAC, stage or location of the primary tumor. IDH mutations were less likely to be found in rectal or sigmoid tumors.

Supplementary Table 5. Patient treatment for IBD

Patient Number	IBD Type	Salicylates	Steroids	anti-TNF	Cytotoxics
1	CD	Treatment data not available			
2	CD	X			
3	CD				
4	CD	X			
5	CD		X		
6	CD				
7	CD		X		
8	CD	X	X	X	X
9	CD		X		
10	CD	X			
11	CD	X	X		
12	CD	X			
13	CD				
14	CD	X			
15	CD	X			
16	CD	X			
17	CD	Treatment data not available			
18	CD				
19	UC	Treatment data not available			
20	UC			X	
21	UC	X			
22	UC	X			
23	UC	X	X		
24	UC	X	X		X
25	UC	X			
26	UC	X	X		
27	UC	X			
28	UC	X			
29	UC				
30	UC	X		X	
31	UC	X	X		
32	UC				
33	UC	Treatment data not available			
34	UC		X		
35	UC		X		
36	UC	X			
37	UC	X	X		
38	UC				
39	UC	X	X		

40	UC	X			
41	UC	X			
42	UC	X			
43	UC				
44	UC	X			
45	UC				X
46	UC			X	
47	UC	X	X		

Salicylates include sulfasalzine and mesalamine; steroids include budesonide, prednisone, and dexamethasone; cytotoxics include 6-mercaptopurine, azathioprine, and methotrexate; and anti-TNF agents include infliximab or adalimumab. Case numbers match order of cases in the oncoprint in Figure 1.

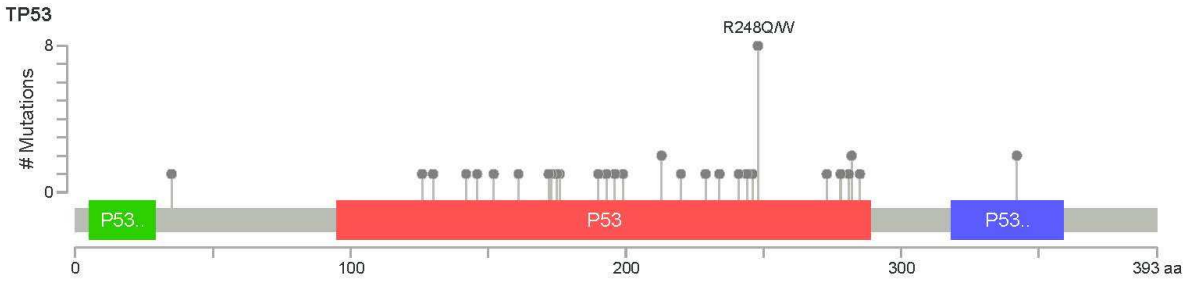
Supplementary Table 6. Comparison of Genomic Alterations Frequency in CAC in the current report, using NGS, with Genomic Alterations frequency in the same genes using whole exome analysis as reported by Robles *et al* (reference 21).

Gene	%mut CAC current study	%mut CAC Robles	%mut TCGA-CRC
TP53	89	63	52
KRAS	40	20	42
SMAD4	17	13	14
SMAD2	2	10	8
SOX9	2	10	5
PIK3CA	6	10	15
PREX2	0	10	6
APC	21	13	76
EP300	0	10	6
MTOR	2	10	7
GNAS	13	NR	11
IDH1	11	NR	1

NR – not reported.

Supplementary Figure Legends

Supplementary Figure 1 - Mutation map showing the location of *TP53* mutations in the sequenced CAC cases. The different domains of *TP53* are marked in color: p53 transactivation motif (amino acids 5-29) in green, p53 DNA-binding domain (amino acids 95-289) in red, and p53 tetramerisation motif (amino acids 318-359) in blue. The height of the lollipops in the plot corresponds to the number of cases with each *TP53* variant, as indicated on the y-axis.


TP53
R248Q/W
8
Mutations
0
P53..
P53
P53..
0
100
200
300
393 aa