Supplementary material

Long-term outcomes of pouch surveillance and risk of neoplasia in familial adenomatous polyposis

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Table 1s: Differences in surveillance between patients who had a primary pouch (RPC) versus those who had a secondary pouch RPC. Medians, ranges, and interquartile ranges (IQR) provided for each variable. P-values derived from Mann Whitney U-tests.

	All of follow-up		
	Primary RPC (n=164)	**Secondary RPC (n=85)**	**P value**
Number of surveillance exams	7 (range 1-24, IQR = [4,12])	11 (range 1-26, IQR= [5,16])	0.001
Mean surveillance interval	1.54 years (range 0.14 – 15.93, IQR = [1.19- 2.46])	1.32 years (range 0.52 – 5.75, IQR = [1.09-1.81])	0.019
Patient age at first surveillance exam	34 years (range 6 - 77, IQR = [25-43])	40 years (range 17-71, IQR = [34-48])	1.2e-05
Pouch age at first surveillance exam	3.84 years (range 0.14 -30.85, IQR = [1.41-10.34])	2.81 years (range 0.55-18.38, IQR = [1.26-8.08])	0.363
Patient age at last surveillance exam	43 years (range 10-81, IQR=[32-52])	53 years (range 25-83, IQR = [44-61])	8.2e-08
Pouch age at last surveillance exam	14.41 years (range 0.14-37.31, IQR = [8.27-21.33])	17.07 years (range 0.76-34.56, IQR = [9.79-22.26])	0.196

**Figure 1s: Surveillance outcomes and overlap in pouch body and cuff.**

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A) Kaplan-Meier curve for progression to first adenoma in pouch body. Median survival (dotted line) was 10.4 years (95% CI [9.6–11.0])
B) Kaplan-Meier curve for progression to first adenoma in cuff. Median survival (dotted line) was 11.4 years (95% CI [10.1–13.4]) since pouch surgery (pouch age).
C) Venn diagram showing that most patients develop pouch body adenomas also develop cuff adenomas
D) Venn diagram to show that advanced lesions seem to occur as separate phenomena in patients (with an overlap of only 12 patients)
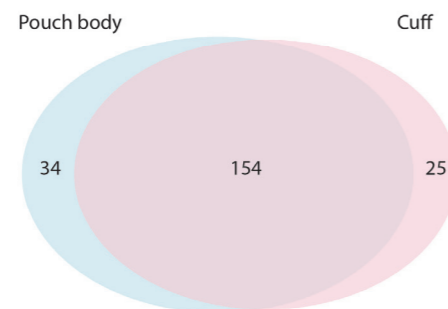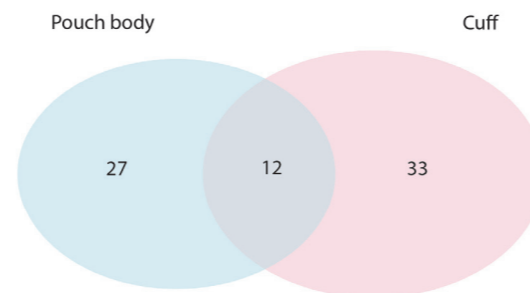
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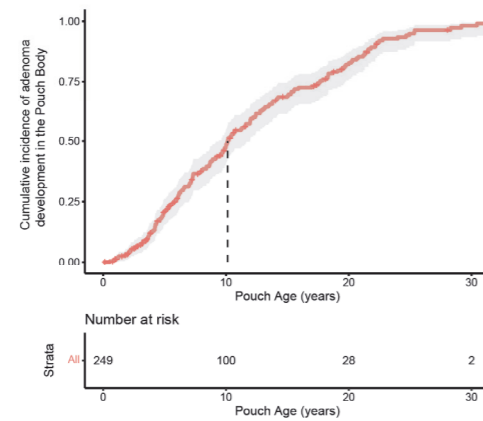
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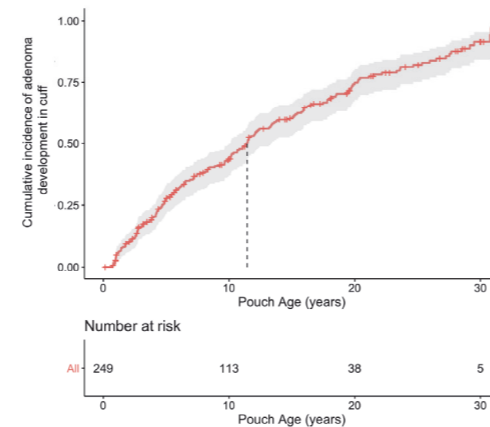
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Table 2s: Development of any adenoma or advanced lesion in the pouch body.

Univariate analyses for progression to any adenoma and advanced lesion (defined by size =>10mm or HGD/ cancer) from baseline pouch surgery
- Risk factors for progression to any adenoma (UNIVARIATE Cox regression analysis – 188/249 progress to an any adenoma [AA])
- Risk factors for progression to an advanced lesion (UNIVARIATE Cox regression analysis – 39/249 progress to an advanced lesion [AL])

Statistical significance in univariate analyses required p<0.01 by either a pragmatic approach or with Bonferroni multiple testing correction considering 5 potential variables. One time-varying covariate (TVC) for Spigelman score analysed (128/249 AA and 32/249 AL progressors included with Spigelman stage recorded before AL or censoring). MCR = Mutation cluster region.

Multivariate analyses for progression to an advanced lesion (AL) from baseline pouch surgery
- Risk factors for progression to >1cm size adenoma *and/or* HGD/CRC (MULTIVARIATE Cox regression analysis – 39/249 AL)
- Risk factors for progression to >1cm size adenoma *and/or* HGD/CRC for patients with Spigelman stage (MULTIVARIATE with TVC– 32/207 AL)

Variable	Any adenoma			Advanced Lesion								
	Univariate			Univariate			Multivariate			Multivariate with TVC		
	Number	Hazard ratio (95 % CI)	P	Number (n=249)	Hazard ratio (95% CI)	P value	Number (n=249)	Adjusted Hazard ratio (95% CI)	P value	Number (n=207)	Adjusted Hazard ratio (95% CI)	P value
Female sex	118 / 249	0.8 (0.6 – 1.1)	0.133	118 / 249	0.6 (0.3 – 1.1)	0.119	118 / 249	0.6 (0.3 – 1.3)	0.190	94/ 207	0.7 (0.3 – 1.6)	0.470
Age at pouch surgery (years)	(n=249)	1.01 (1.001-1.027)	0.033	(n=249)	1.0 (0.99-1.1)	0.176	(n = 249)	1.0 (0.97 – 1.04)	0.860	(n = 207)	1.0 (0.97 – 1.04)	0.793
APC mutation type	(n = 249)			(n = 249)			(n = 249)			(n = 207)		
- 1250 − 1450 (MCR)	69	1	ref	69	1	ref	69	1	ref	54	1	ref
- 1 − 1249	152	1.1 (0.8 – 1.5)	0.663	152	1.5 (0.7 – 3.3)	0.315	152	1.5 (0.7 – 3.5)	0.320	135	1.4 (0.6 – 3.1)	0.486
- > 1450	20	1.5 (0.9 – 2.7)	0.138	20	4.3 (1.4-13.5)	0.013	20	4.4 (1.3 – 15.3)	0.019	14	0.7 (0.1 – 6.1)	0.741
- Gross deletion	8	0.9 (0.4 – 2.2)	0.873	8	-	1.0	8	-	1.0	4	-	0.997
Type of initial pouch surgery	(n = 249)			(n = 249)			(n = 249)			(n = 207)		
- IRA (secondary RPC)	85	1	ref	85	1	ref	85	1	ref	80	1	ref
- Primary RPC	164	0.9 (0.7 – 1.2)	0.522	164	0.8 (0.4 – 1.5)	0.516	164	0.7 (0.3 – 1.3)	0.256	127	0.9 (0.4 – 2.0)	0.864
Baseline Spigelman stage	(n = 80; 57 AA)			(n = 80; 11 AL)			-			-		
- 0	13	1	ref	13	1	ref						
- 1	20	0.9 (0.4 – 2.0)	0.719	20	0.4 (0.0 – 5.9)	0.475						
- 2	29	1.3 (0.6 – 2.9)	0.572	29	2.1 (0.2 – 17.3)	0.498						
- 3+	18	0.9 (0.4 – 2.3)	0.853	18	1.2 (0.1 – 13.2)	0.892						
Spigelman stage (time-varying covariate; max)	(128 AA)			(32 AL)			-			(32 AL)		
- 0		1	ref		1	ref					1	ref
- 1		1.4 (0.7 – 2.8)	0.365		1.0 (0.2 – 6.3)	0.969					1.1 (0.2 – 6.8)	0.925
- 2		1.6 (0.8 – 2.9)	0.161		1.0 (0.2 – 4.7)	0.995					0.9 (0.2 – 4.5)	0.929
- 3+		1.9 (1.01 – 3.6)	0.048		1.9 (0.4– 8.4)	0.395					1.7 (0.4 – 8.0)	0.490

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Table 3s: Development of adenoma and advanced lesion in cuff.
Univariate analysis for progression to any adenoma and advanced lesion in the cuff from baseline pouch surgery
- Risk factors for progression to any adenoma detected (UNIVARIATE Cox regression analysis – 179/249 progress to an adenoma [AA])
- Risk factors for progression to >1cm size adenoma *and/or* HGD/CRC (UNIVARIATE Cox regression analysis – 45/249 progressed to advanced lesion [AL]).
Statistical significance in univariate analyses required p<0.01 by either a pragmatic approach or with Bonferroni multiple testing correction considering 5 potential variables (denoted by red values). MCR = Mutation cluster region.
Multivariate analysis for progression to advanced lesion in the cuff from baseline pouch surgery
- Risk factors for progression to >1cm size adenoma *and/or* HGD/CRC (MULTIVARIATE Cox regression analysis – 19/151 AL)

Variable	Any Adenoma			Advanced Lesion					
	Univariate			Univariate			Multivariate		
	Number (n=249)	Hazard ratio (95% CI)	P value	Number (n=249)	Hazard ratio (95% CI)	P value	Number (n=151)	Adjusted Hazard ratio (95% CI)	P value
Female sex	118 / 249	0.8 (0.6 − 1.1)	0.105	118 / 249	0.8 (0.4 − 1.5)	0.478	66 / 151	0.7 (0.3 − 2.0)	0.511
Age at pouch surgery (years)	(n=249)	1.01 (0.99-1.02)	0.137	(n = 249)	1.01 (0.99 − 1.04)	0.245	(n = 151)	1.06 (1.01 − 1.11)	0.026
APC pathogenic variant type	(n = 249)			(n = 249)			(n = 151)		
- 1250 − 1450 (MCR)	69	1	ref	69	1	ref	43	1	ref
- 1 − 1249	152	1.3 (0.9-1.8)	0.144	152	1.6 (0.7 − 3.6)	0.234	94	1.0 (0.3 − 3.2)	0.994
- >1450	20	2.1 (1.2-3.6)	0.010	20	5.2 (1.9 − 14.2)	0.001	8	1.0 (0.1 − 8.0)	0.967
- Gross deletion	8	0.9 (0.4-2.1)	0.827	8	1.7 (0.4 − 8.2)	0.493	6	-	0.998
Type of initial pouch surgery	(n = 249)			(n = 249)			(n = 151)		
- IRA (secondary RPC)	85	1	ref	85	1	ref	60	1	ref
- Primary RPC	164	1.1 (0.8-1.5)	0.586	164	1.2 (0.7-2.3)	0.506	91	0.7 (0.3-2.2)	0.589
Type of anastomosis	(n = 151; 108 AA)			(n = 151; 19 AL)			(n = 151; 19 AL)		
- Handsewn	72	1	ref	72	1		72	1	ref
- Stapled	79	3.5 (2.3-5.2)	<0.001	79	4.5 (1.7 − 11.9)	0.002	79	5.9 (2.0 − 17.1)	0.001

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Table 4s: Clinical characteristics of cases of high grade dysplasia and cancer in pouch

Patient age at RPC	Gender	Diagnosis	Genotype	Anastomosis	Shape	Year of pouch surgery	Pouch age at start of surveillance	Pouch age at 10mm lesion	Location	Pouch age at HGD/cancer diagnosis	Year of HGD/Cancer Diagnosis	Interval from last benign examination (months)	Symptoms	Mode of diagnosis	Management	Histopathology	Chemo/rad	Survival
42	Male	FAP	codon 1132; sequence 3394 G >T	Handsewn	J	1995	5y10m	5y10m	Cuff	7y11m	2003	7	No	Histopathology	EUA and surgical excision of cuff lesion	HGD	N/A	
									Cuff	19y7m	2015	4 (decision to proceed to surgery due to circumferential adenoma)	No	Histopathology PE specimen	APE	Moderately differentiated adenocarcinoma; pT3 N0 (0/27) V0 MX R1	Nil	Alive
17	Female	FAP	codon 452; sequence 1355 ins GT	Handsewn	J	1988	11y1m	21y7m	Cuff	30y3m	2018	7 (decision made to proceed to surgery due to circumferential lesion at cuff)	No - PE for large cuff polyp. Polyp cancer found on specimen	Histopathology PE specimen	APE	Moderately differentiated mucinous adenocarcinoma; pT1 N0 (0/23) MX V0 L0 Pn0 R0	Nil	Alive
23	Male	FAP	codon 1309; sequence 3927 - 3931 del AAAGA	Unknown	Unknown	2003	7y5m	7y5m	Cuff	11y7m	2015	11	No	At surveillance	Exenteration	Moderately differentiated adenocarcinoma; ypT2 N0 (0/13) V0 R0	Neoadjuvant chemotherapy	Alive
11	Female	FAP	codon 1491; sequence 4473 del T	Handsewn	Unknown	1992	19y6m	19y10m	Cuff	20y4m	2012	3 (decision made to proceed to PE due to circumferential lesion at cuff)	No	Histopathology PE specimen	APE	HGD	NA	Alive
22	Female	FAP & Crohn's disease	codon 554; sequence 1660 C > T	Stapled	Unknown	1987	30y10m	N/A as patient diagnosed with cuff cancer at index surveillance	Cuff	30y10m	2018	No prior surveillance	Bleeding and anal pain	Diagnosed at index pouchoscopy	Exenteration	Moderately differentiated adenocarcinoma; T2 N0 Pn1 V0 R0	Neoadjuvant chemo-radiation	Alive
24	Male	FAP and Ulcerative colitis	codon 1122; sequence 3366 - 3369 del TCAA	Unknown	Unknown	1984	30y5m	30y5m	Pouch body	34y5m	2018	6 (called back as had poor bowel preparation)	No	At surveillance	No surgery; palliative care as presented with extensive metastasis	Nil	Nil	12 months

*APE = abdominoperineal excision, y= years, m= months, PE = pouch excision

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Table 5s: Differences in surveillance between patients who progressed to advanced lesions ('progressors') and patients who did not progress to an advanced lesion ('non-progressors') during follow-up in the pouch body or cuff. For patients who developed an advanced lesion (AL), surveillance data is included until date of development of an advanced lesion. Medians, ranges, and interquartile ranges (IQR) provided for each variable. P-values derived from Mann Whitney U-tests.

	Pouch body			Cuff		
	Non-progressors (n=210)	Progressors to AL (n=39)	P value	Non-progressors (n=204)	Progressors to AL (n=45)	P value
Number of surveillance exams	7 (range 1-25, IQR = [4,13])	8 (range 1-23, IQR= [2,13])	0.785	8 (range 1-21, IQR =[4-13]	4 (range 1-17, IQR = [2,9]	0.002
Mean surveillance interval	1.46 years (range 0.14 – 16, IQR = [1.26-5.39])	1.96 years (range 0.66 – 30.44, IQR = [1.29-5.39])	0.006	1.5 years (range 0.14-10.56, IQR = [1.16-2.24]	1.97 years (range = 0.72-30.85, IQR = 1.23-6.12)	0.008
Patient age at first surveillance exam	35 years (range 6 - 77, IQR = [27-45])	40 years (range 18-61, IQR = [33-48])	0.039	35 years (range 6 - 77, IQR = [27-45])	40 years (range 18-61, IQR = [33-48])	0.039
Pouch age at first surveillance exam	2.73 years (range 0.14 -30.85, IQR = [1.24-8.16])	8.54 years (range 0.92-30.44, IQR = [3.93-12.24])	7.9e-05	2.73 years (range 0.14 -30.85, IQR = [1.24-8.16])	8.54 years (range 0.92-30.44, IQR = [3.93-12.24])	7.9e-05
Patient age at last surveillance exam	45 years (range 10-83, IQR=[34-55])	48 years (range 26-76, IQR = [40-57])	0.173	45 years (range 10-81, IQR = [34-55])	42 years (range 22-80, IQR =[36-53]	0.657
Pouch age at last surveillance exam	14.15 years (range 0.14-34.63, IQR = [6.88-19.66])	15.9 years (range 0.92-33.72, IQR = [12.33-22.16])	0.025	14.53 years (range 0.14-37.31, IQR = [7.12-21.45])	11.89 years (range 0.97-34.45, IQR = [8.06-19.73]	0.668

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Table 6s: Clinical details of ten patients who had pouch excision for benign neoplasia.

#	Sex	RPC			Pouch Excision		Histopathology from pouch excision						Survival		
		Age at RPC	Anastomosis	Primary histology	Patient age	Indication	Number of pouch body polyps	Number of cuff polyps	Greatest size of adenoma in pouch body mm	Greatest size of polyp in cuff	Greatest histology pouch body	Greatest histology in cuff	Age at death	Cause of death	Age at last follow-up
1	M	32	unknown	malignancy	46	adenoma burden in cuff and pouch body, 666 adenomas in pouch	666	unknown	7	unknown	LGD	LGD	55	metastatic gastric cancer	RIP
2	M	43	stapled	benign	59	increasing and concerning development of adenomas both within the cuff and body of the pouch	the entire pouch covered in adenomas	the entire pouch is covered in adenomas	10	unknown	LGD	LGD	61	metastatic gastric cancer	RIP
3	M	38	handsewn	malignancy	56	high adenoma burden in pouch body	330	0	3	NA	LGD	NA	64	metastatic duodenal cancer	RIP
4	M	36	stapled	malignancy	52	cuff carpetting (primarily excised for poor function)	scattered adenomas	carpetted	7	6	LGD	LGD	NA	NA	58
5	M	19	unknown	unknown	40	adenoma burden in cuff and pouch body	>100	1	30	12	LGD	LGD	NA	NA	58
6	M	41	handsewn	unknown	60	carpetting in pouch body	carpetting	unknown	8	unknown	LGD	NA	NA	NA	61
7	F	37	handsewn	benign	50	high adenoma burden in pouch body	332	0	90	NA	LGD	NA	NA	NA	63
8	M	54	handsewn	unknown	64	large adenoma in the pouch body	11	unknown	95	3	LGD	LGD	NA	NA	67
9	M	30	unknown	unknown	40	large adenoma in the pouch body	68	15	30 to 40	10	LGD	LGD	NA	NA	48
10	F	11	unknown	unknown	32	high adenoma burden in pouch body and cuff	150	numerous	15	15	LGD	HGD	NA	NA	40