Agenda

Topics of the day

- Use of molecular markers in surveillance — Rodrigo Jover (Spain)
- FIT for surveillance — Joaquin Cubiella (Spain)
- Who deserves surveillance? Selection of patients at the highest risk after polyp removal — Emma Robbins (UK)

WEO

The voice of world endoscopy

Use of molecular markers as predictors of metachronous neoplasia

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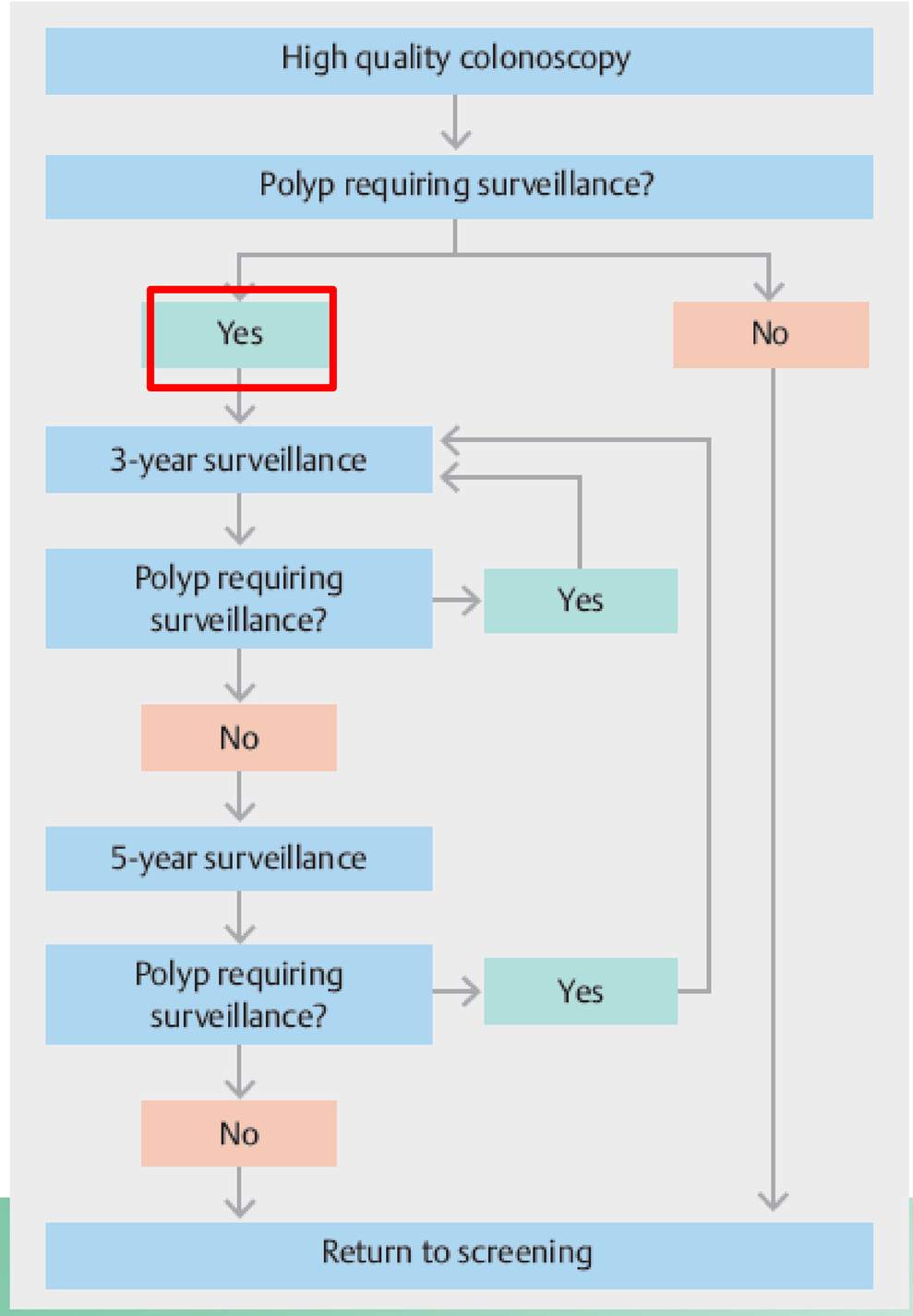
SURVEILLANCE

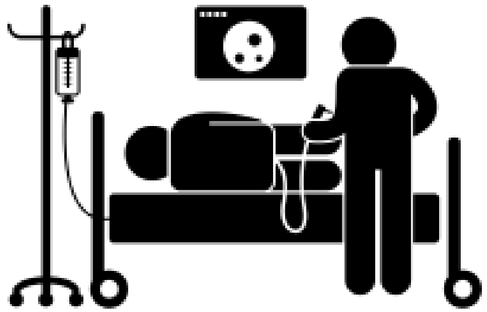
ADENOMAS

- Any adenoma ≥ 1 cm
- ≥ 5 adenomas
- High grade dysplasia

SERRATED POLYPS

- ≥ 1 cm
- With dysplasia





Surveillance

- Size of lesions: reflects molecular and genetic impairment
- Number of lesions: reflects potential colonic factors, potential quality aspects
- Pathology factors: reflects molecular and genetic development

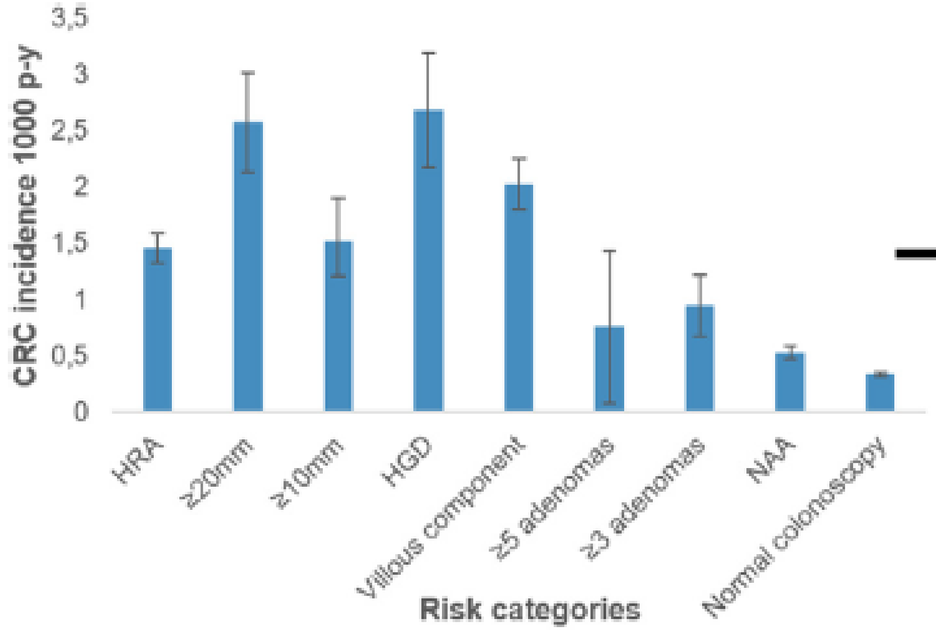
- Can we go beyond classical risk factors???

Why people with polyps excised are at a higher risk of developing new lesions?

1. Overlooked lesions: Suboptimal quality of baseline procedure

2. Field effect: there is “something” in the “normal” colonic mucosa

Some high risk factors select patients at the highest risk



Risk category	RR for CRC risk	
	Compared with NAA	Compared with normal colonoscopy
HRA	2.56 [2.21-2.96]	2.92 [2.29-3.73]
Size ≥ 20mm	3.81 [2.19-6.63]	
Size ≥ 10mm	1.66 [1.30-2.13]	2.61 [2.06-3.32]
HGD	2.89 [1.88-4.44]	6.62 [4.60-9.52]
Villous component	1.75 [1.33-2.31]	3.58 [2.24-5.73]
≥ 5 adenomas	1.36 [0.54-3.46]	
≥ 3 adenomas	1.24 [0.84-1.83]	2.03 [1.40-2.94]

Clinical Gastroenterology and Hepatology

Baile-Maxía, CGH 2023

Why molecular markers can be better than traditional risk factors?

- Markers that summarize the real risk factor beyond size and number of lesions
- Molecular markers can reflect the reason for the risk of developing new or multiple lesions
- Perhaps these markers can help to select people at the highest risk

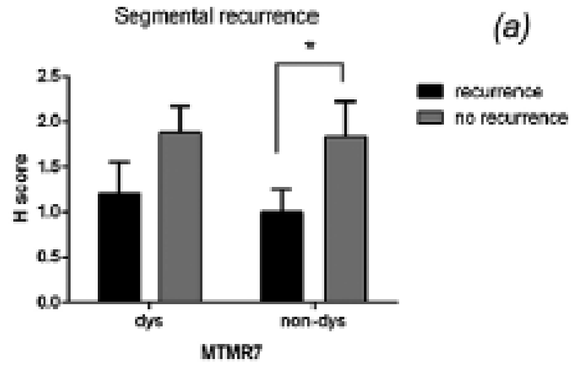
DOK1-MTMR7

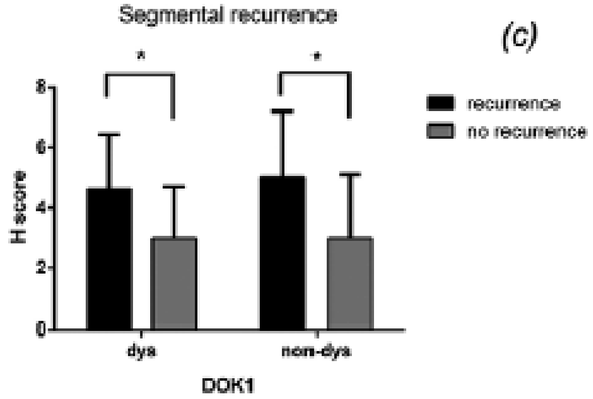
Tumor suppressors EGFR-RAS pathway

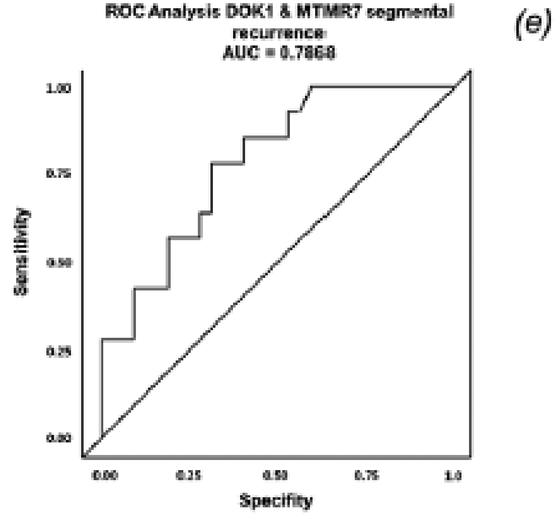
Table IV. Logistic regression using a stepwise selection model for segmental recurrence

Stepwise selection model of logistic regression for segmental recurrence							
Case-related analysis of DOK1 & MTMR7							
	Tissue type	Odds ratio	95%CI	Coefficient	SE	p value	ROC AUC
DOK1	Non-dysplastic	1.62	1.1–1.39	0.482	0.199	0.0155 *	0.78
MTMR7	Non-dysplastic	0.57	0.95–1.98	-0.561	0.286		
Adenoma-related analysis of MTMR7							
	Tissue type	Odds ratio	95% CI	Coefficient	SE	p value	ROC AUC
MTMR7	Dysplastic	0.43	0.22 – 0.84	-0.846	0.340	0.0129 *	0.76

Confidence level 95%. CI: confidence interval, SE: standard error, ROC: receiver operator characteristics, AUC: area under the curve. * = $p < 0.05$.

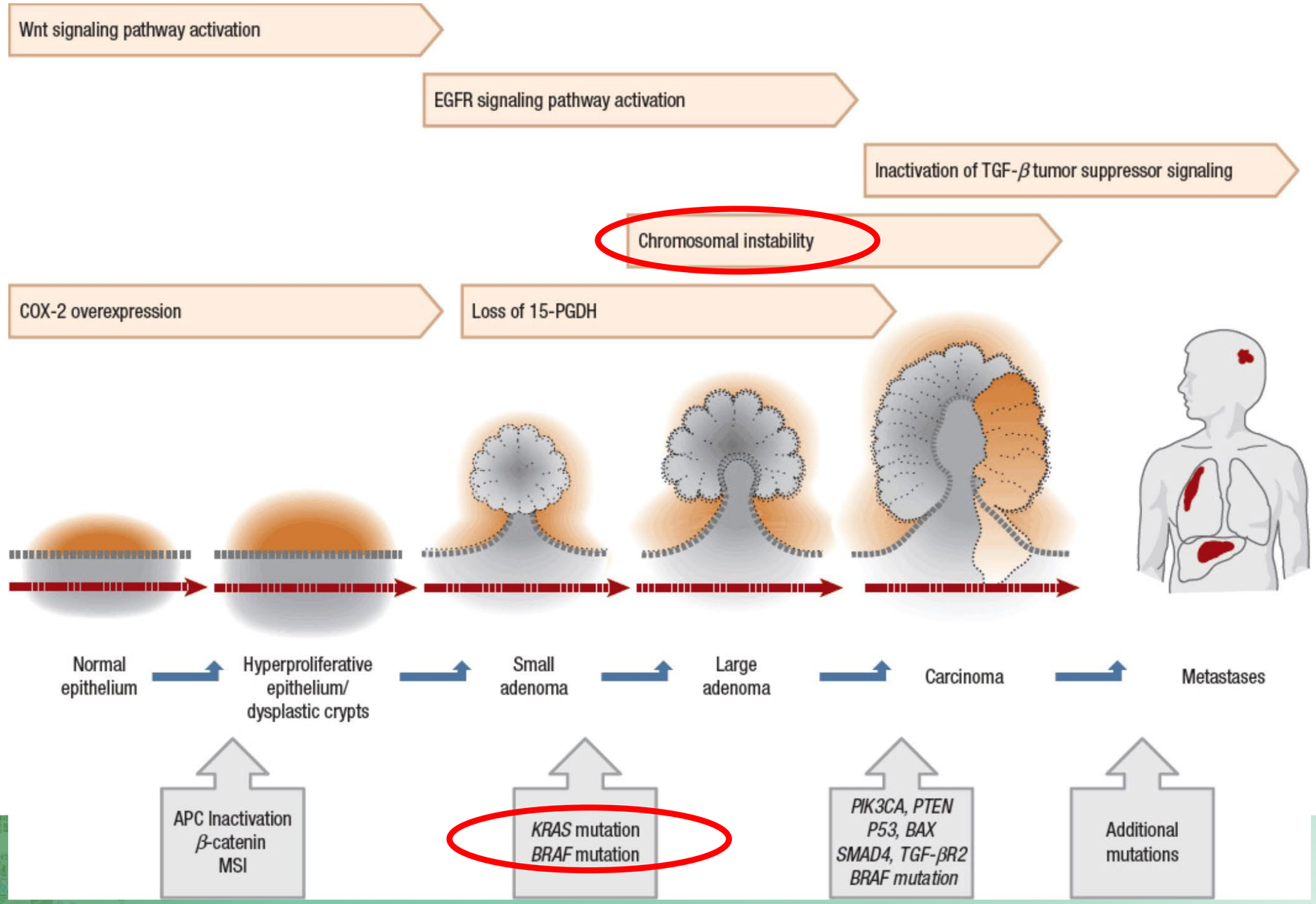




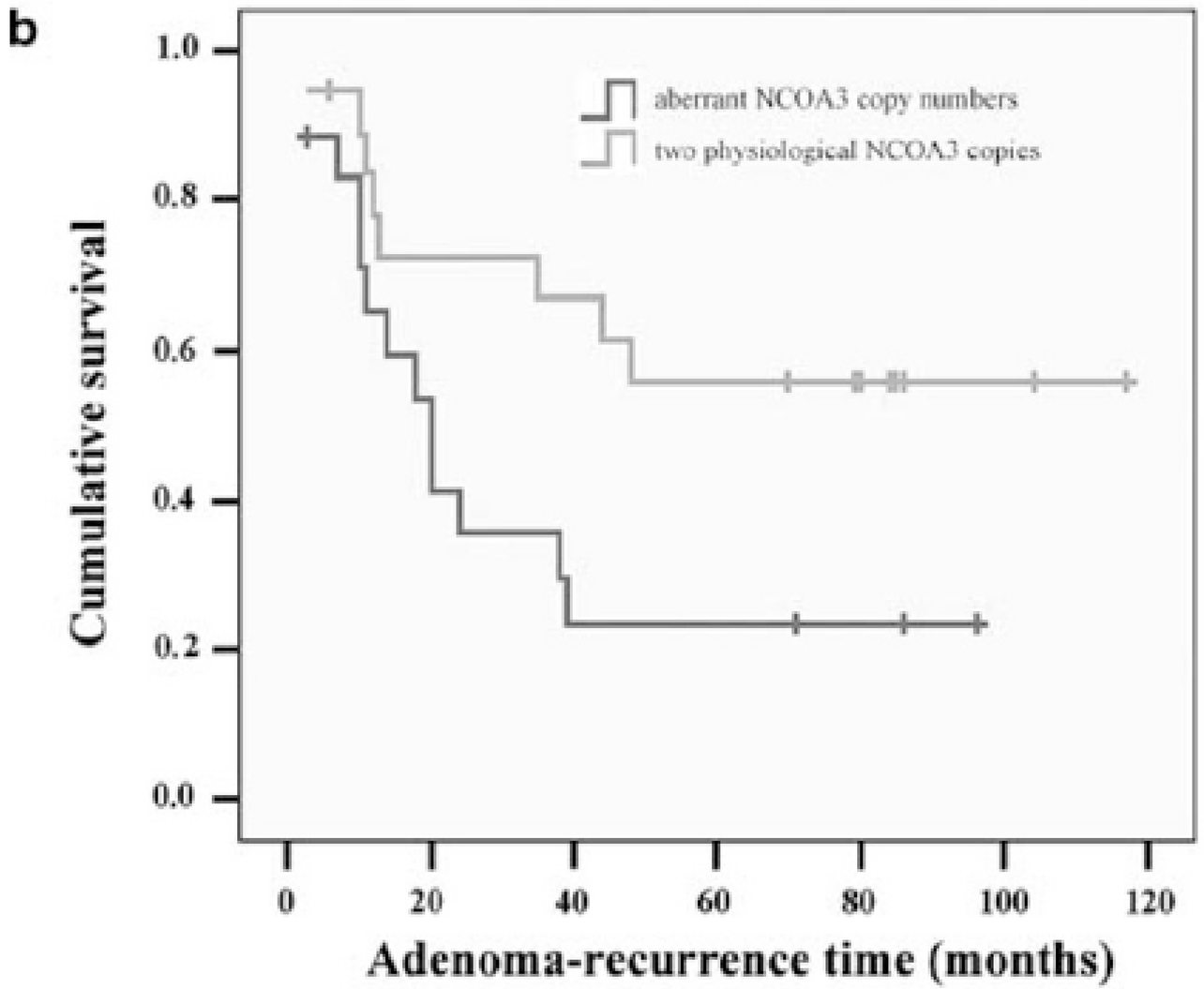


Gutting, J Gastrointest Liv Dis 2021

Chromosomal instability pathway

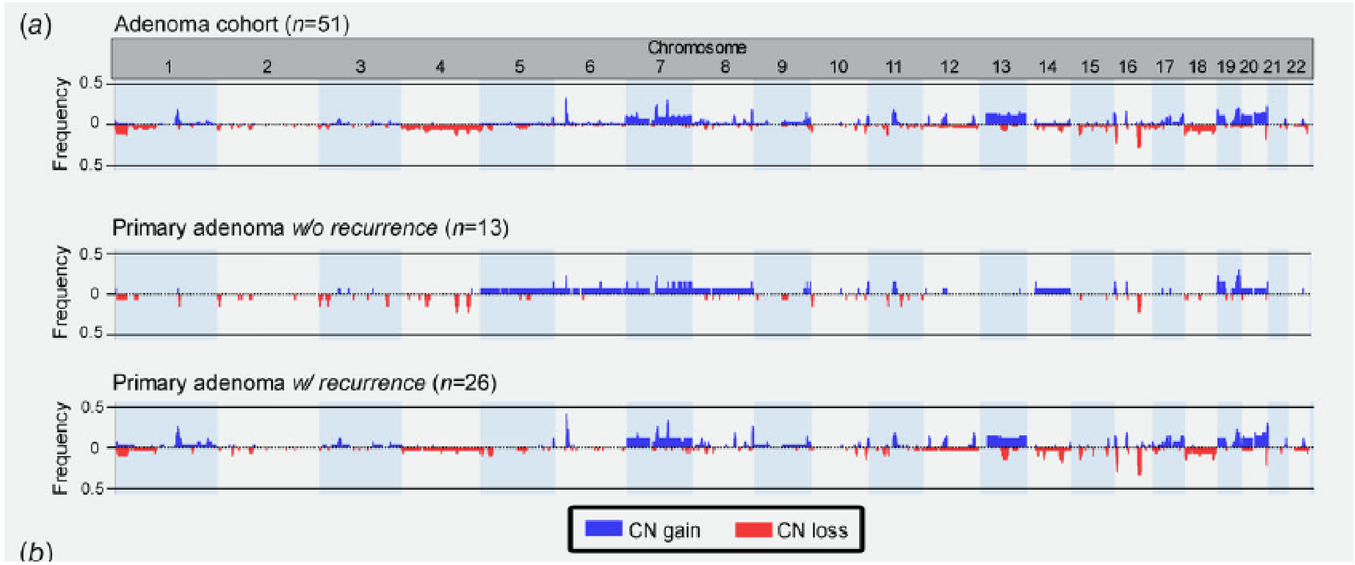


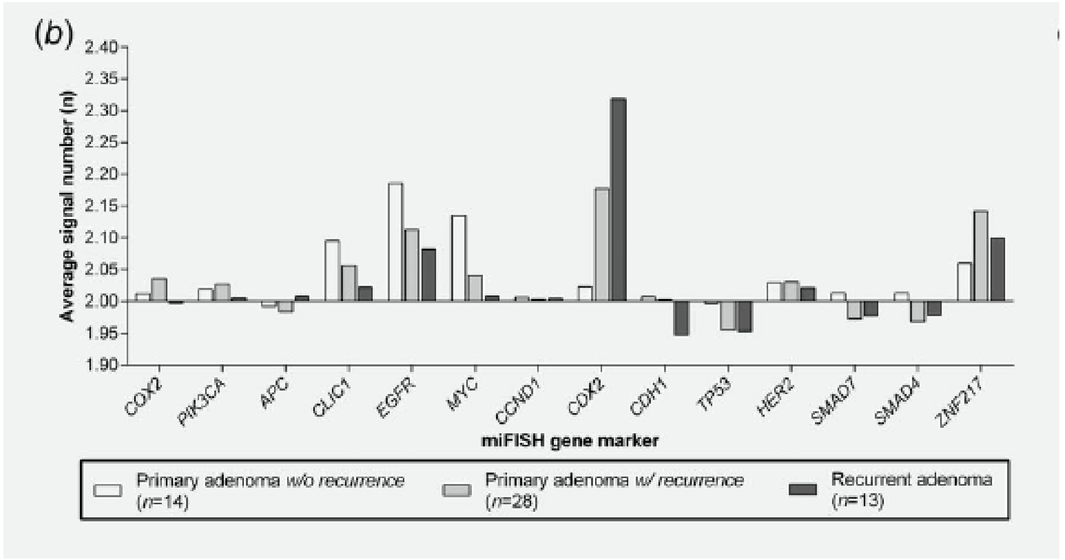
CNVs



Habermann, Modern Pathol 2011

CNVs





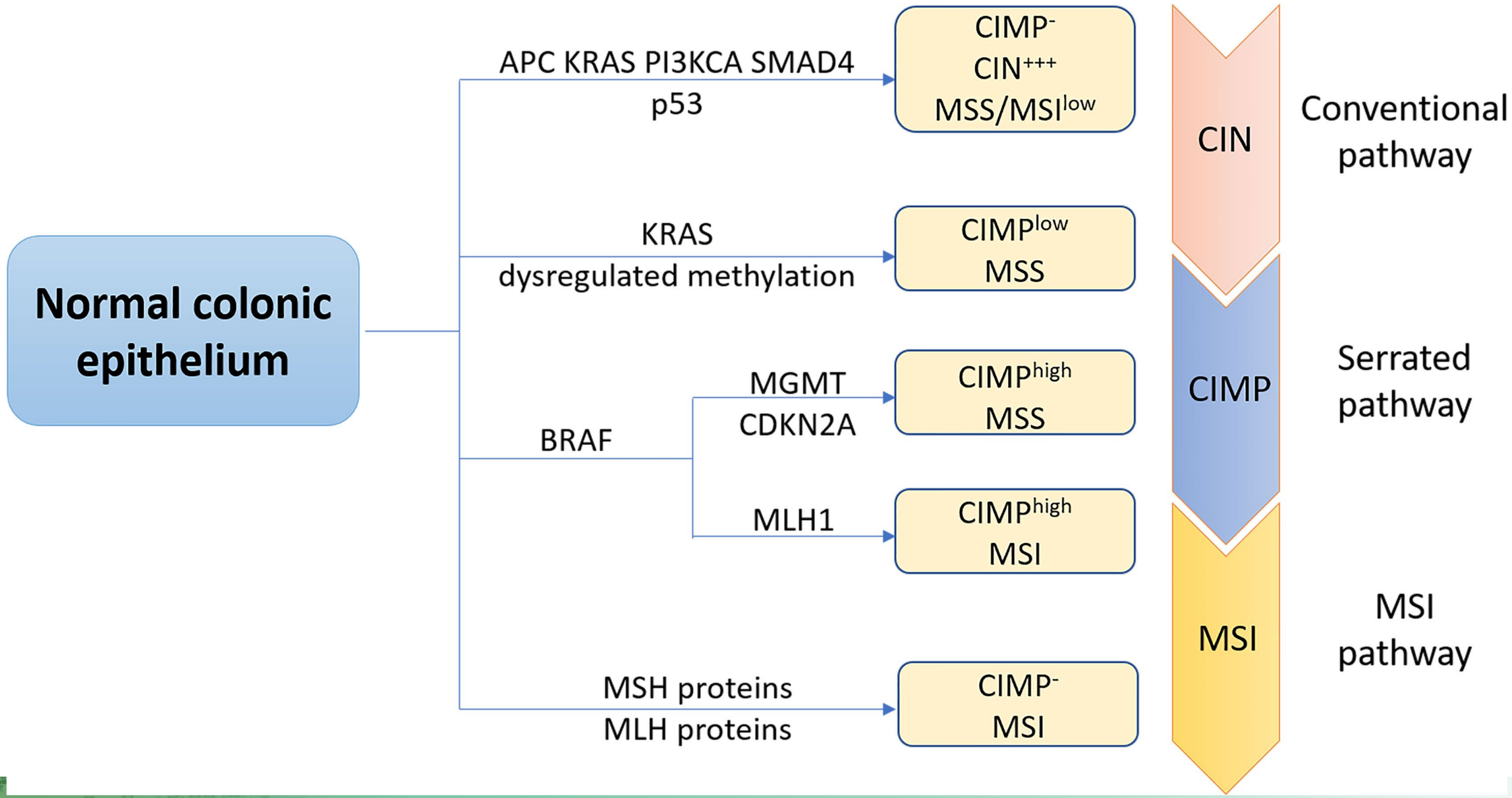
Fiedler, Int J Cancer 2019

MLH1

Table 5. **Predictive factors of metachronous risk lesions (multivariate analysis)**

	Surveillance colonoscopy				
Basal characteristics	**AAs OR (95% CI)**	**Proximal AA OR (95% CI)**	**≥3 polyps OR (95% CI)**	**High risk lesions (AA and/or multiplicity) OR (95% CI)**	**Large serrated lesions OR (95% CI)**
Age 60–69	1.55 (0.76–3.14)	3.59 (1.29–9.93)	1.34 (0.71–2.54)	1.51 (0.87–2.60)	0.91 (0.27–3.21)
Gender (female)	2 (1–4)	3.12 (1.31–7.69)	1.21 (0.60–2.45)	1.40 (0.77–2.53)	2.84 (0.73–11.05)
Smoker/former	1.74 (0.85–3.58)	0.95 (0.38–2.33)	1.64 (0.85–3.20	1.69 (1.00–2.86)	4.82 (1.05–22.02)
Dyslipidemia	1.03 (0.53–2.02)	0.86 (0.37–2.01)	2.47 (1.33–4.57)	1.68 (1.00–2.79)	0.71 (0.20–2.45)
≥3 polyps	3.01 (1.44–6.27)	4.42 (1.66–11.75)	2.93 (1.48–5.81)	2.35 (1.35–4.10)	3.70 (0.81–16.83)
>1 colonoscopy	1.21 (0.56–2.57)	1.82 (0.72–4.64)	1.74 (0.90–3.38)	1.64 (0.92–2.93)	3.64 (1.16–11.34)
Adenoma size ≥20 mm	0.92 (0.41–2.09)	0.69 (0.23–2.02)	0.94 (0.46–1.94)	1.04 (0.56–1.93)	2.33 (0.68–8.8.03)
NRAS	1.23 (0.25–6.07)	1.87 (0.35.9.93)	1.05 (0.18–5.96)	1.08 (0.26–4.49)	4.45 (0.43–46.51)
MLH1	3.06 (0.57–16.21)	15.21 (3.07–76.58)	4.09 (0.88–18.95)	4.03 (0.99–16.43)	

Carot, Clin Transl Gastroenterol 2021

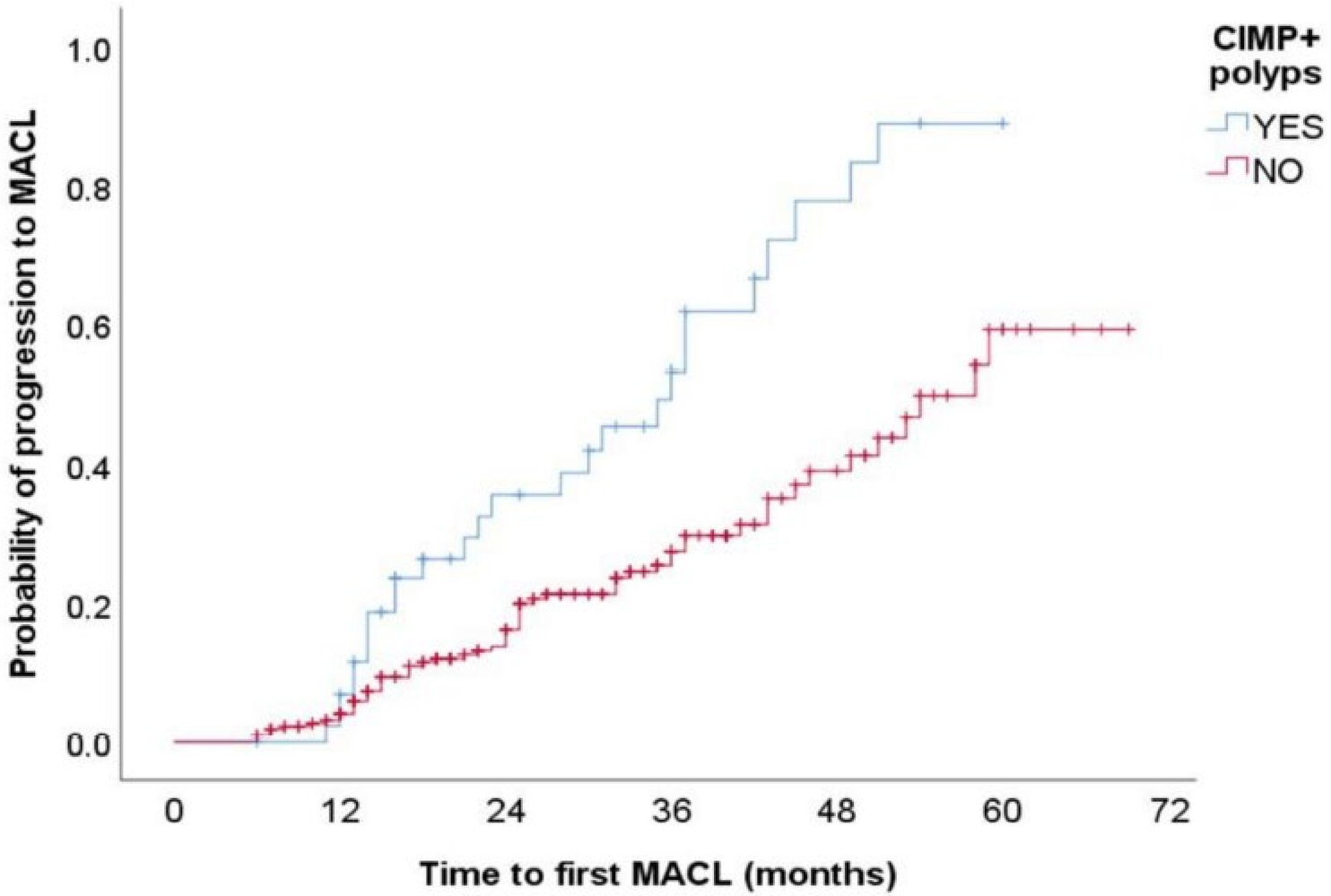

Normal colonic epithelium
APC KRAS PI3KCA SMAD4
p53
CIMP-
CIN+++
MSS/MSIlow
KRAS
dysregulated methylation
CIMPlow
MSS
BRAF
MGMT
CDKN2A
CIMPhigh
MSS
MLH1
CIMPhigh
MSI
MSH proteins
MLH proteins
CIMP-
MSI
CIN
CIMP
MSI
Conventional pathway
Serrated pathway
MSI pathway

Serrated polyps: MLH1

Molecular characteristics	Among index SSA/Ps, $n = 169$					Among index right-sided SSA/Ps only, $n = 137$				
	Cases n (%)	Controls n (%)	Adjusted OR[a]	95% CI		Cases n (%)	Controls n (%)	Adjusted OR[b]	95% CI	
BRAF mutation										
Wildtype	6 (35)	42 (28)	1.00	Ref		3 (25)	29 (24)	1.00	Ref	
Mutant	11 (65)	110 (72)	0.74	0.24	2.27	9 (75)	90 (76)	0.78	0.18	3.34
CIMP										
No	8 (47)	79 (48)	1.00	Ref		6 (50)	50 (40)	1.00	Ref	
Low	6 (35)	66 (40)	0.98	0.32	3.03	3 (25)	60 (48)	0.53	0.12	2.43
High	3 (18)	18 (11)	1.67	0.38	7.33	3 (25)	15 (12)	1.30	0.33	5.19
MLH1 methylation										
PMR ≤ 10	15 (88)	156 (97)	1.00	Ref		10 (83)	121 (98)	1.00	Ref	
PMR > 10	2 (12)	5 (3)	4.66	1.06	20.51	2 (17)	3 (2)	6.00	2.12	16.95

Hua, Cancer Causes Control 2020

CIMP


Probability of progression to MACL
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
Time to first MACL (months)
CIMP+ polyps
YES
NO

KRAS restrospective study

Table 4. Multivariate analysis of clinical and molecular characteristics of patients, adjusted for age and sex.

OUTCOME	OR	95% CI		*P*-value
Factors included in the analysis		**Min.**	**Max.**	
ADVANCED ADENOMAS				
Molecular Classification				
-Wild-type Group	1			
-*BRAF* Group	0.99	0.31	3.12	1.0
-*KRAS* Group	2.23	1.02	4.85	**0.044**
ADVANCED SERRATED LESIONS				
No Previous CRC	1			
Previous CRC	2.17	0.85	5.53	0.1
Adenomas Size <10 mm or no adenomas	1			
Adenomas Size ≥10 mm	0.40	0.15	1.05	0.1
ANY ADVANCED POLYP				
Molecular Classification				
-Wild-type Group	1			
-*BRAF* Group	1.08	0.43	2.71	0.9
-*KRAS* Group	2.27	1.15	4.46	**0.018**

Juárez, PLOSone 2017

KRAS

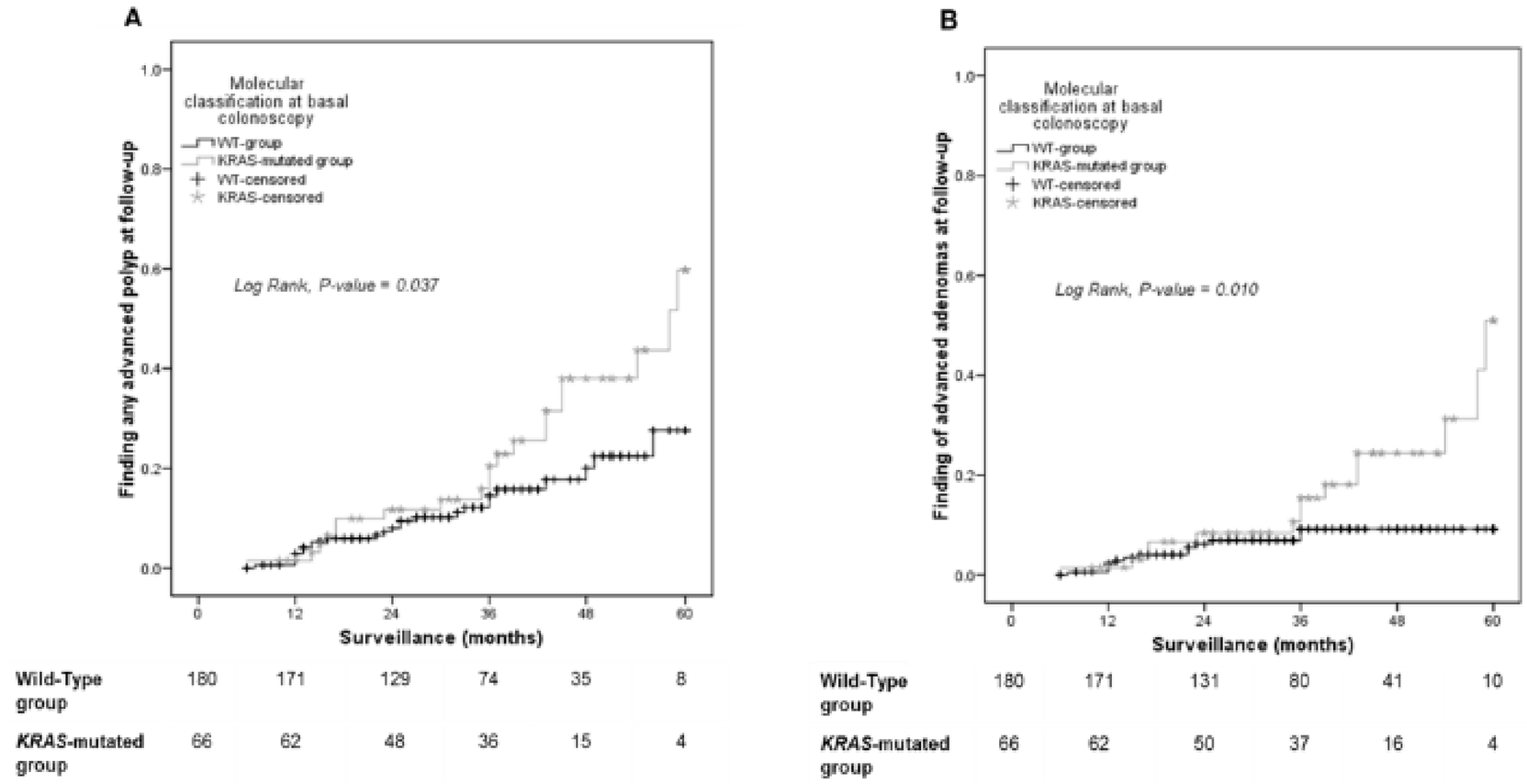


Fig 2. Risk of developing advanced polyps based on *KRAS* mutational status at baseline colonoscopy. Kaplan-Meier curves show the proportions of patients with WT or *KRAS*-mutated lesions that developed either (A) any advanced polyp or (B) advanced adenomas over time.

Juárez, PLOSone 2017

BRAF retrospective

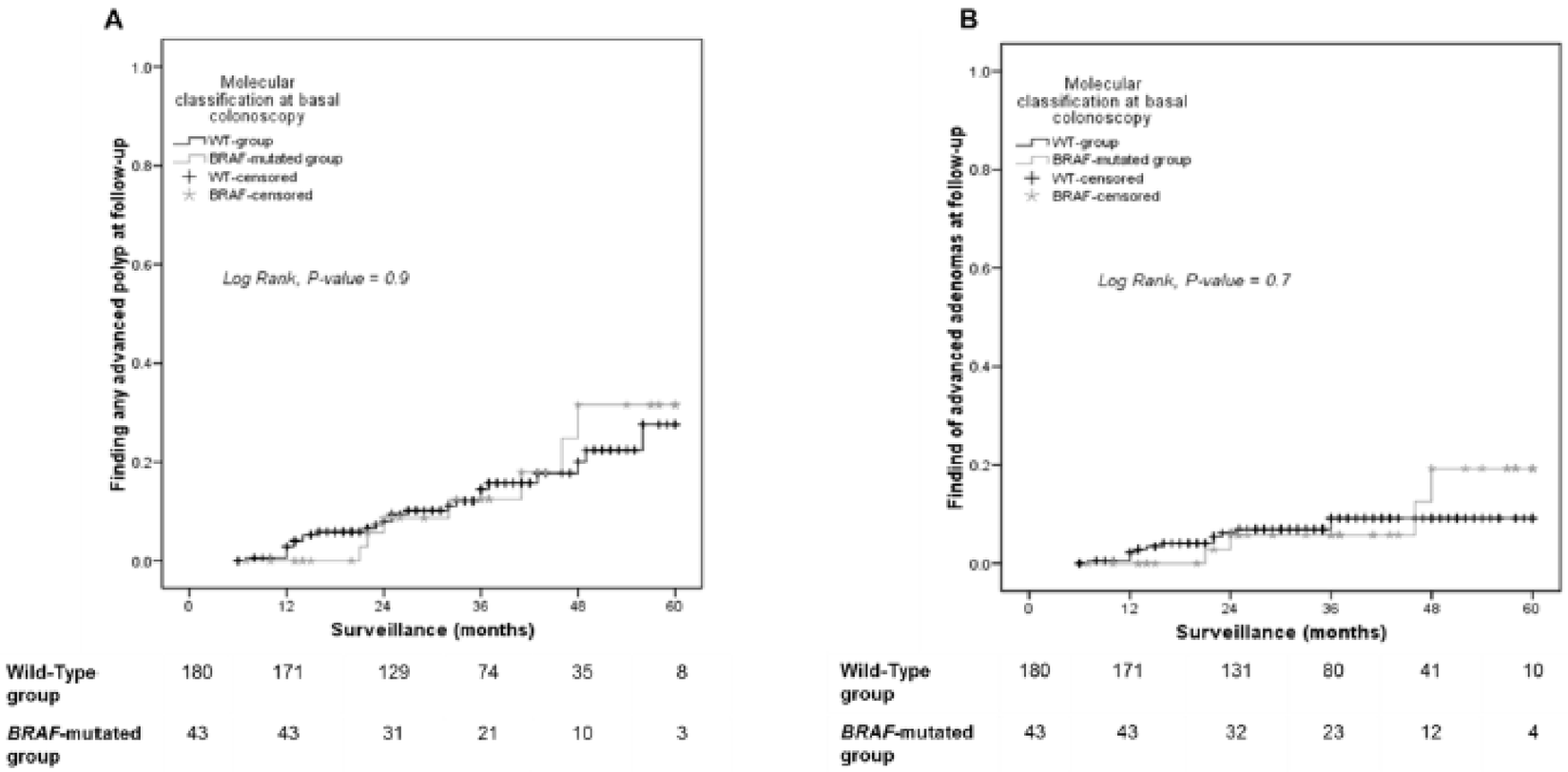
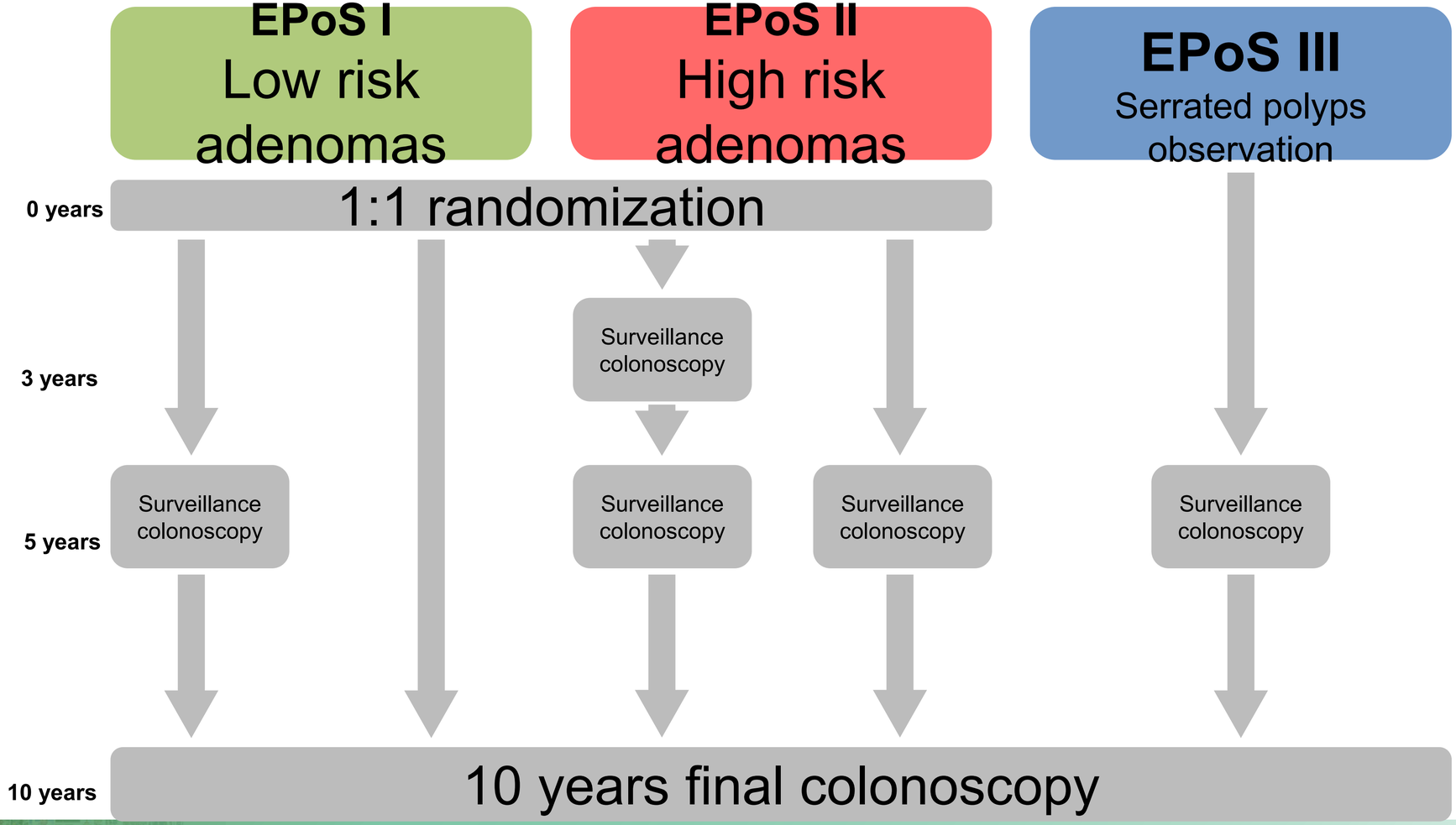


Fig 1. Risk of developing advanced polyps based on *BRAF* mutational status at baseline colonoscopy. Kaplan-Meier curves show the proportions of patients with WT or *BRAF*-mutated lesions that developed either (A) any advanced polyp or (B) advanced adenoma over time.

Juárez, PLOSone 2017

EPoS trials
European Polyp Surveillance



KRAS prospective
EPoS II-3 years
518 patients with high-risk adenomas

	KRAS WILD-TYPE 1099 (92.4%)	KRAS MUTATED 90 (7.6%)
TYPE OF ADENOMA		
Tubular	782 (95.2%)	39 (4.8%)
Tubulo-villous	176 (79.6%)	45 (20.4%)
Villous	6 (75.0%)	2 (25.0%)
SIZE		
<10	688 (96.8%)	23 (3.2%)
10-19	345 (88.2%)	46 (11.8%)
≥20	66 (75.9%)	21 (24.1%)
DYSPLASIA		
High	31 (79.5%)	8 (20.5%)
Low	1068 (92.9%)	82 (7.1%)
ADVANCED ADENOMA		
Yes	460 (86.0%)	75 (14.0%)
No	639 (97.7%)	15 (2.3%)

Martínez-Roca, UEGW 2022

KRAS prospective

	Univariate Analysis		Multivariate Analysis
Characteristics at baseline		**OR (95%CI)**	**OR (95%CI)**
Age, median (IQR)	**67 (61-70)**	**1.06 (1.02-1.10)**	**1.06 (1.03-1.11)**
Sex, n (%)			
Male	84 (25.4)	1	
Female	35 (18.7)	1.47 (0.95-2.30)	
HISTOLOGY, n (%)			
Serrated lesions	25 (29.1)	1	
Adenomas	94 (21.8)	1.47 (0.87-2.47)	
ADVANCED SERRATED POLYPS, n (%)			
No	111 (22.2)	1	1
Yes	8 (42.1)	2.54 (1.00-6.47)	2.67(0.97-7.28)
ADVANCED ADENOMA, n (%)			
No	1 (33.3)	1	
Yes	118 (22.9)	0.59 (0.53-6.61)	

Martínez-Roca, UEGW 2022

KRAS prospective

ADENOMA NUMBER, n (%)			
<3	**46 (16.5)**	**1**	**1**
3-4	**41 (23.8)**	**4.54 (2.56-8.33)**	**4.32 (2.36-7.88)**
≥5	**32 (47.1)**	**2.84 (1.56-5.26)**	**2.88 (1.54-5.34)**
PROXIMAL POLYPS, n (%)			
No	39 (16.3)	1	1
Yes	80 (28.9)	2.10 (1.36-3.23)	1.06 (0.62-1.83)
VILLOUS HISTOLOGY, n (%)			
No	73 (22)	1	
Yes	46 (24.7)	1.16 (0.76-1.77)	
≥20MM POLYPS, n (%)			
No	100 (22.5)	1	
Yes	19 (25.7)	1.18 (0.67-2.10)	
HGD, n (%)			
No	112 (23)	1	
Yes	7 (21.9)	0.93 (0.40-2.21)	
KRAS MUTATION, n (%)			
No	**86 (19.5)**	**1**	**1**
Yes	**33 (42.3)**	**3.02 (1.81-5.02)**	**3.30 (1.92-5.65)**

Martínez-Roca, UEGW 2022

Molecular markers for surveillance

- Potential use to go beyond traditional risk markers
- Potentially able to select patients at the highest risk
- Prospective studies
- More research is needed
- Markers of field effect

WEO

World Endoscopy Organization