WEO

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Molecular pathways in post-colonoscopy versus detected colorectal cancers: results from a nested case–control study

Beatriz Carvalho, PhD

The Netherlands Cancer Institute

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Disclosures

No disclosures.

Introduction

- Colonoscopy with polypectomy is not perfect in the prevention of CRC

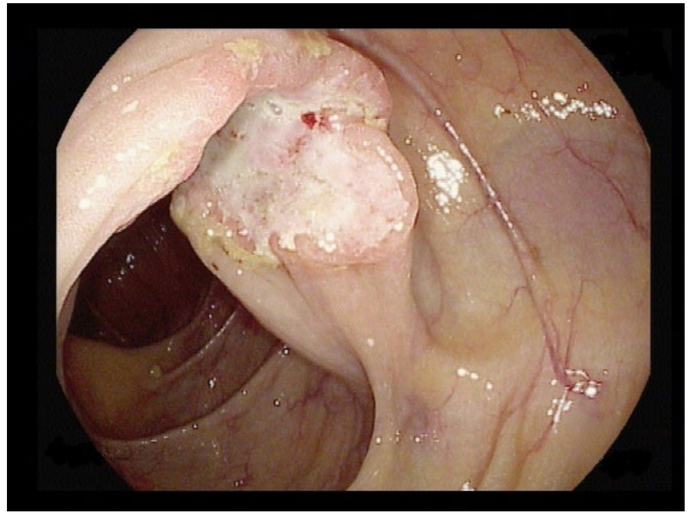
  3.7% (95% CI 2.8-4.9%) of all patients diagnosed with CRC underwent colonoscopy within 5 years[1]

- Postcolonoscopy CRC (PC-CRC)[2]:

  Proximal location

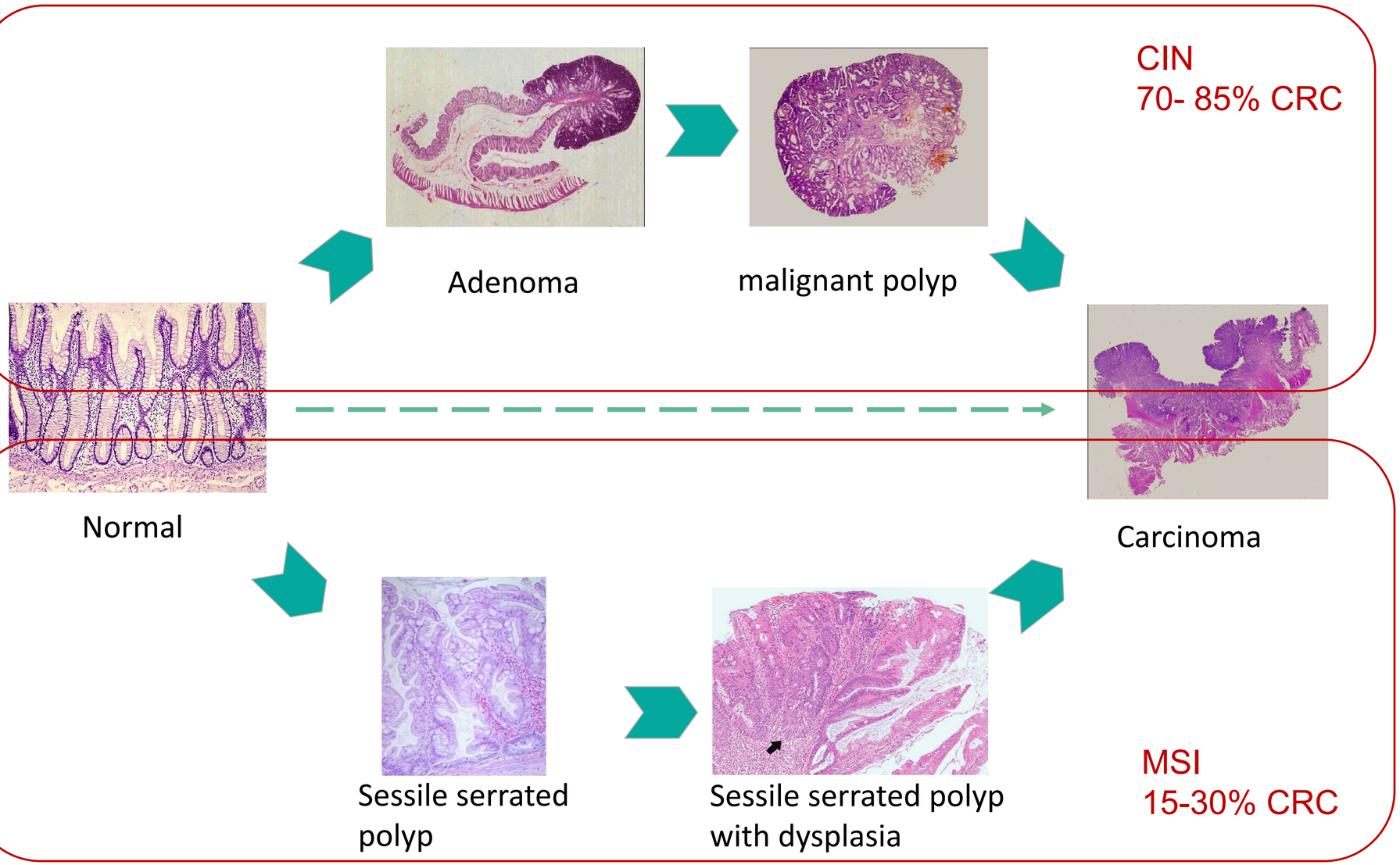
  Flat macroscopic appearance

  Smaller in size



1. Singh …. Samadder. Am J of GE. 2014
2. le Clercq … Sanduleanu. Gut. 2014

Introduction – CRC development



Introduction

Molecular profile of PCCRCs: what do we know?

Author / Publication	Population	PC-CRC vs Detected CRC	P-value
Sawhney et al. Gastroenterology 2006	51 PC-CRCs, 112 prevalent CRCs	MSI: 30.4% vs 10.3%	0.003
Arain et al. Am J Gastro 2009	63 PC-CRCs, 131 prevalent CRCs	CIMP: 57% vs 33%	0.004
Shaukat et al. Dig Dis Sci 2010	63 PC-CRCs, 131 prevalent CRCs	BRAF: 28% vs 19%	0.180
Shaukat et al. Dig Dis Sci 2012	63 PC-CRCs, 131 prevalent CRCs	KRAS: 13% vs 29%	0.030
Nishihara et al. NEJM 2013	62 PC-CRCs, 585 prevalent CRCs	MSI: 25.0% vs. 13.6% CIMP: 30.2% vs. 15.0% BRAF: 21.7% vs. 13.8%	 ns
Richter et al. Dig Dis Sci 2014	42 PC-CRCs, 226 controls	MSI: 40.5% BRAF: 16.7% vs 10.2% KRAS: 28.6% vs 36.7% NRAS: 7.1% vs 4.0% PIK3CA: 16.7% vs 12.4%	 0.280 0.380 0.410 0.460
Woo Lee et al. Gut and Liver 2016	25 PC-CRCs, 261 controls	MSI: 32% vs 8.4%	0.002

Introduction

Non-polypoid CRNs

- Often located in the proximal colon[1]
- Easily overlooked
- Challenging to resect endoscopically
- Distinct molecular features:
  - More often 5q loss[2]
  - More often BRAF mutations[3]
  - Less often 17p & 18q loss[2]
  - Less often APC & KRAS mutations[3]

1. Rondagh, Gastrointest Endosc , 2012; 2. Voorham, Clinical cancer research , 2012; 3.Voorham, Am J Gastroenterol, 2013

Aim

To investigate the molecular profile of PCCRCs, including both the CIN and MSI related mechanisms, in a large population-based cohort

Hypothesis: PCCRCs have a molecular profile that is different from DCRCs, presumably more similar to non-polypoid and/or sessile serrated precursor lesions

Study population

Population-based database 2001-2010
- National pathology database/national cancer registry
- Cross-linkage with hospital data

↓

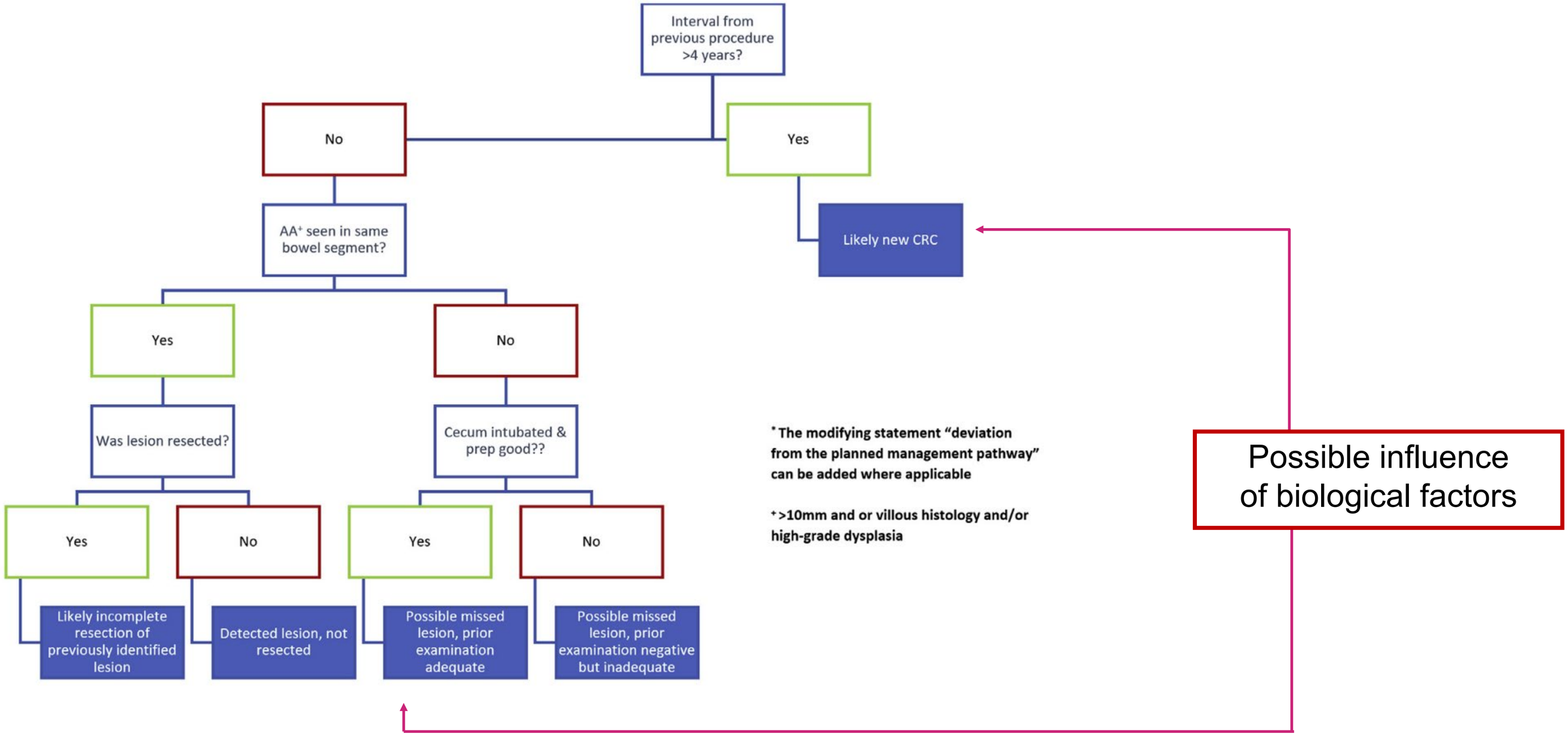
Exclusion of patients with:
- Hereditary CRC
- IBD
- Previous history of CRC

↓

Identification of PCCRCs
Definition: CRCs diagnosed 6 to 60 months after a colonoscopy that was negative for CRC

Le Clercq … Sanduleanu. Gut. 2014

Methods - Most likely etiologic factors



Methods- Molecular analysis

- Whole genome DNA copy numbers

  Low-coverage whole genome sequencing – Illumina

- DNA mutations → 8 most common CRC genes

  Truseq amplicon cancer panel – Illumina

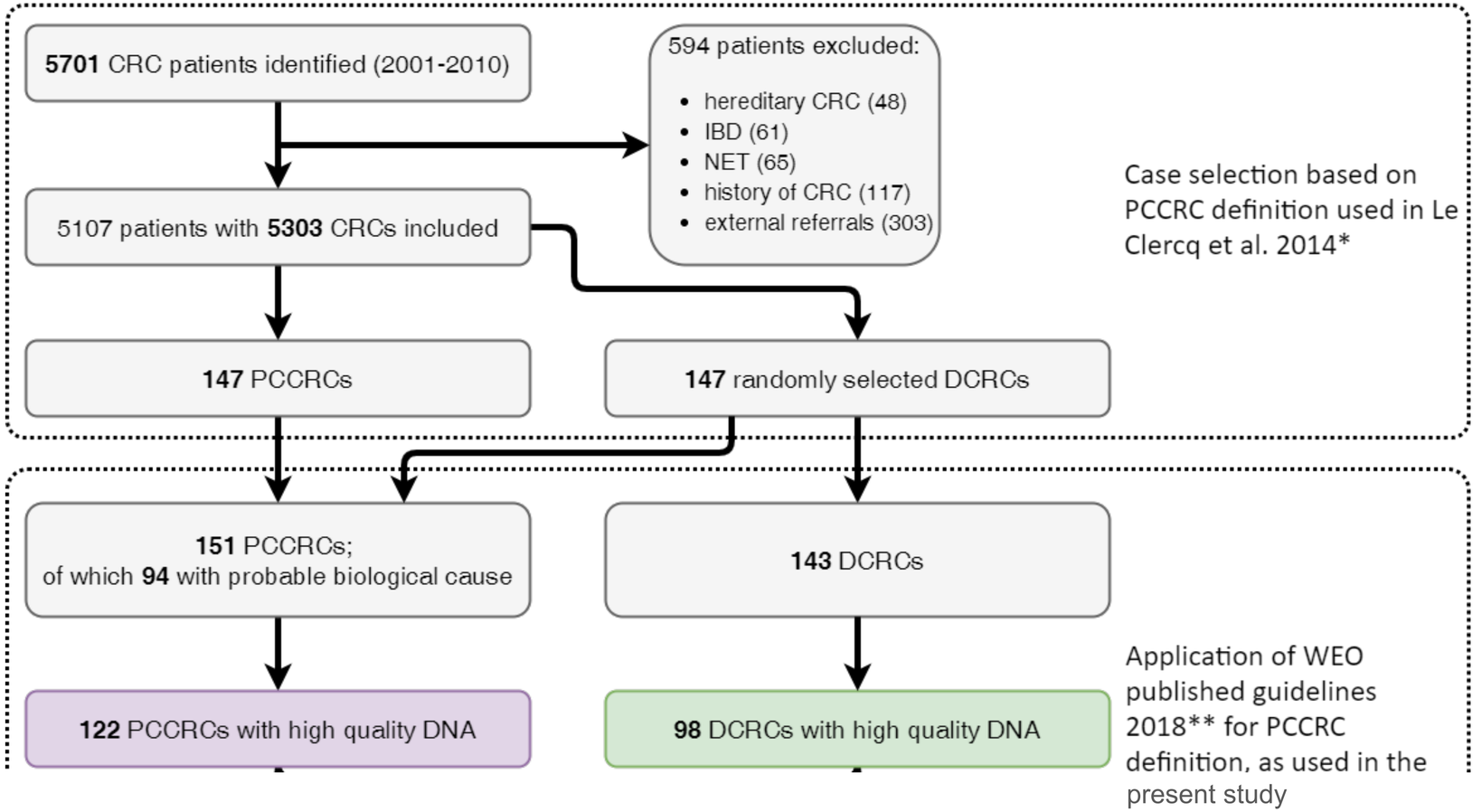
- MSI status

  Pentaplex Promega kit

- CIMP status

  Multiplex MSP – CIMP panel - CACNA1G, IGF2, NEUROG1, RUNX3 and SOCS1 (Weisenberger et al Nat Genet 2006)

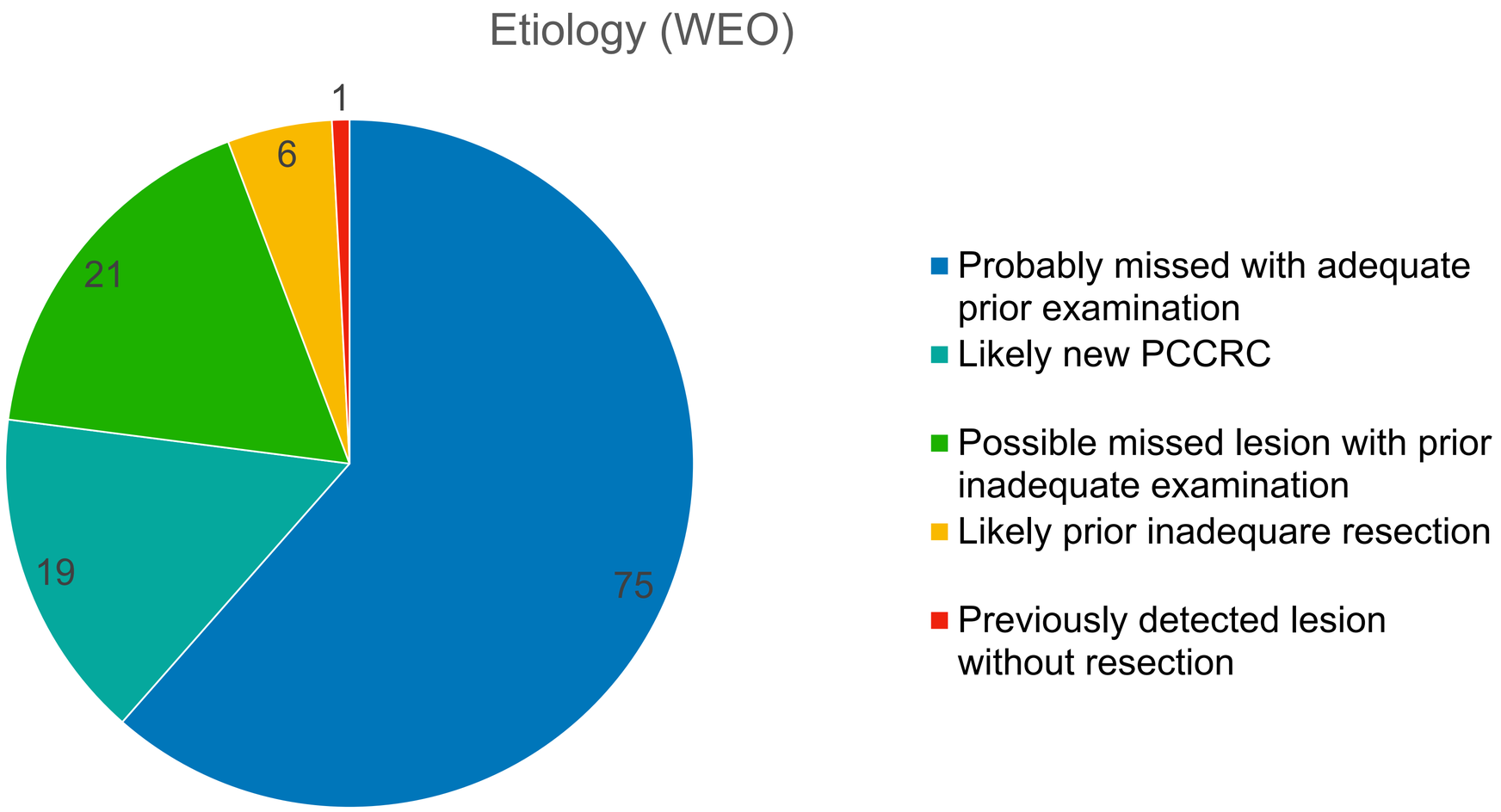
Results – Tumor selection



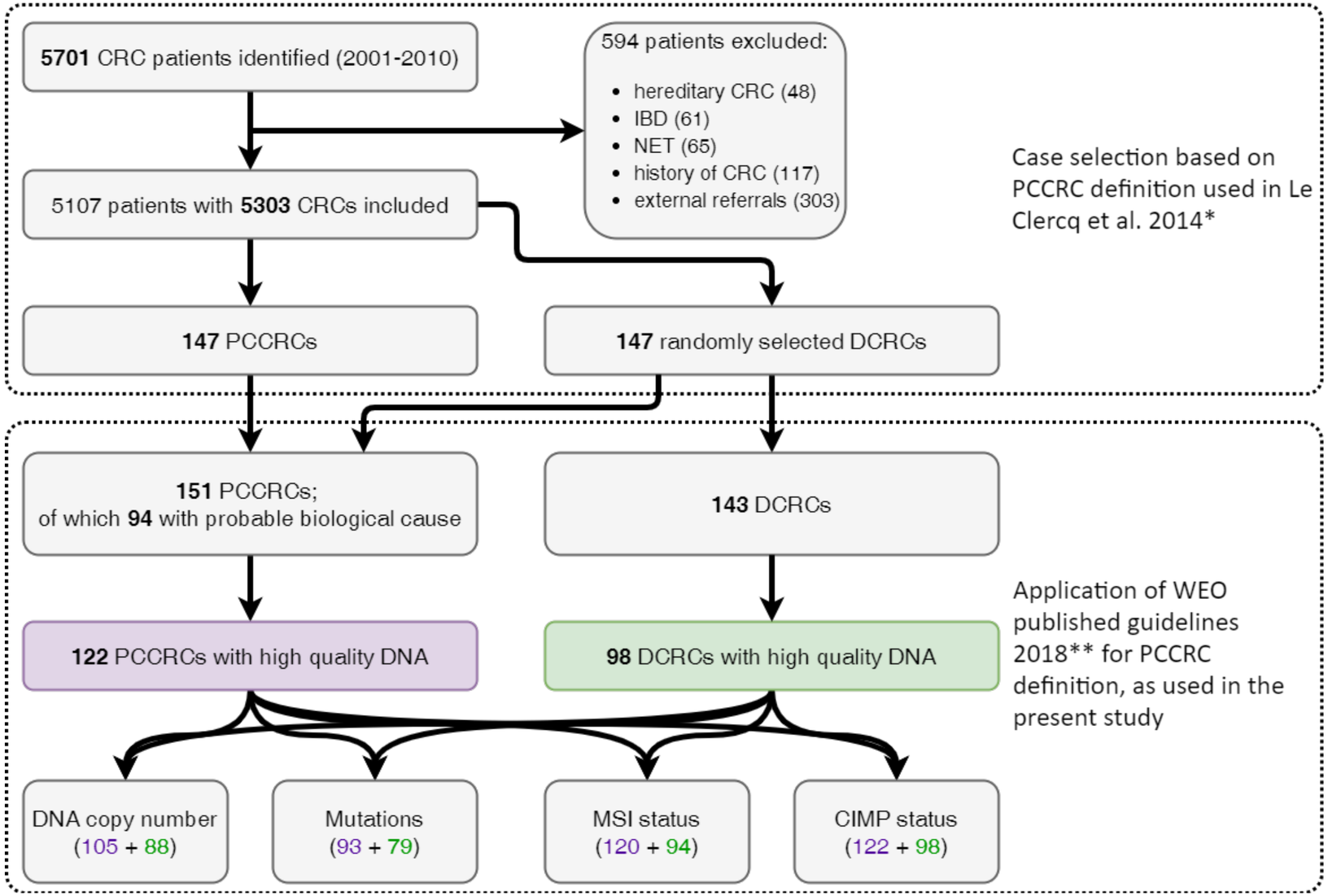
Results – baseline characteristics

Features	PCCRCs (n=122)	DCRCs (n=98)	P value*
Mean age (SD)	71.8 (9.1)	69.4 (11.4)	0.089
Male (%)	70 (57.4)	57 (58.2)	1.000
Current/previous smoking (%)	28 (23.0)	21 (21.9)	0.980
Proximal location (%)	77 (63.6)	31 (31.6)	<0.001
Flat appearance (%)	58 (47.9)	27 (27.8)	0.004
T1 carcinoma (%)	21 (17.6)	5 (5.1)	0.009
Poor differentiation (%)	32 (29.6)	12 (12.8)	0.006
Mucinous histology (%)	17 (13.9)	13 (13.3)	1.000
Diverticulosis (%)	58 (47.5)	20 (20.8)	<0.001
Mean tumour size (SD)	3.6 (1.8)	4.6 (1.9)	<0.001

Results - Etiology of PCCRCs analyzed



Results – Tumor selection and analysis

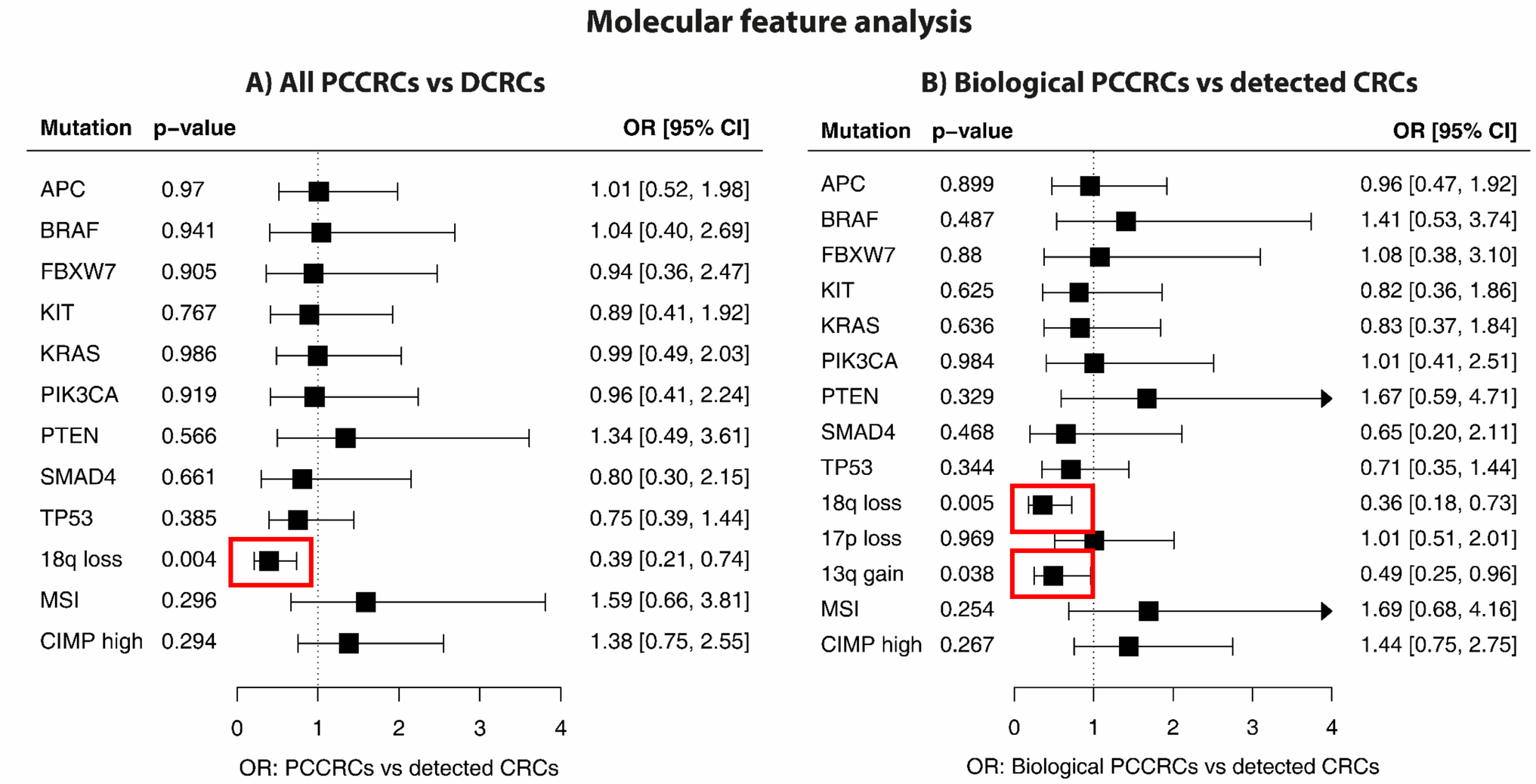


Bogie RMM …Masclee AAM, Carvalho Bl BrJCancer 2022

*Le Clercq … Sanduleanu. Gut. 2014

**Rutter MD, Beintaris I et al. Gastroenterology. 2018

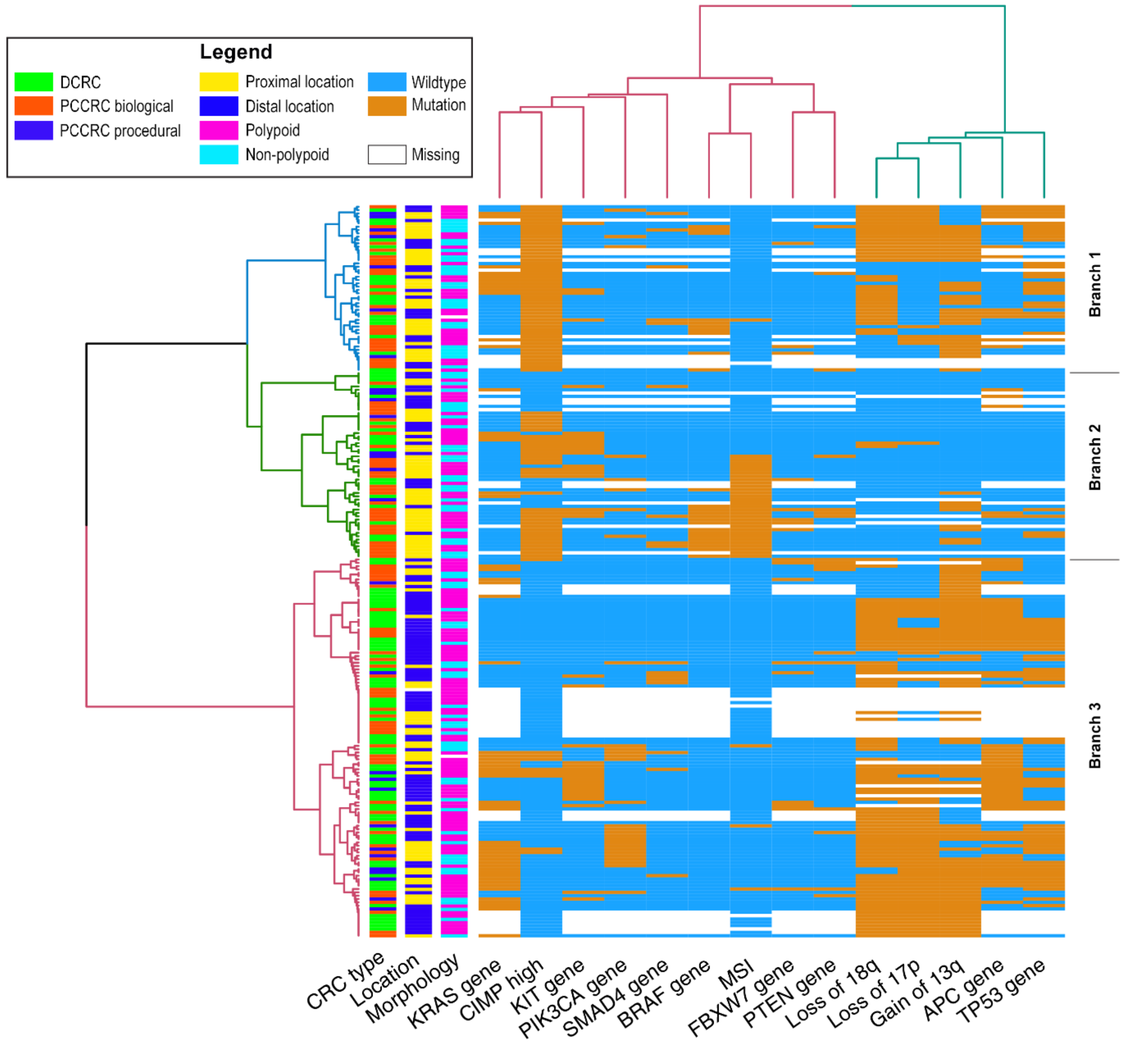
Results- PCCRCs show less copy number alterations



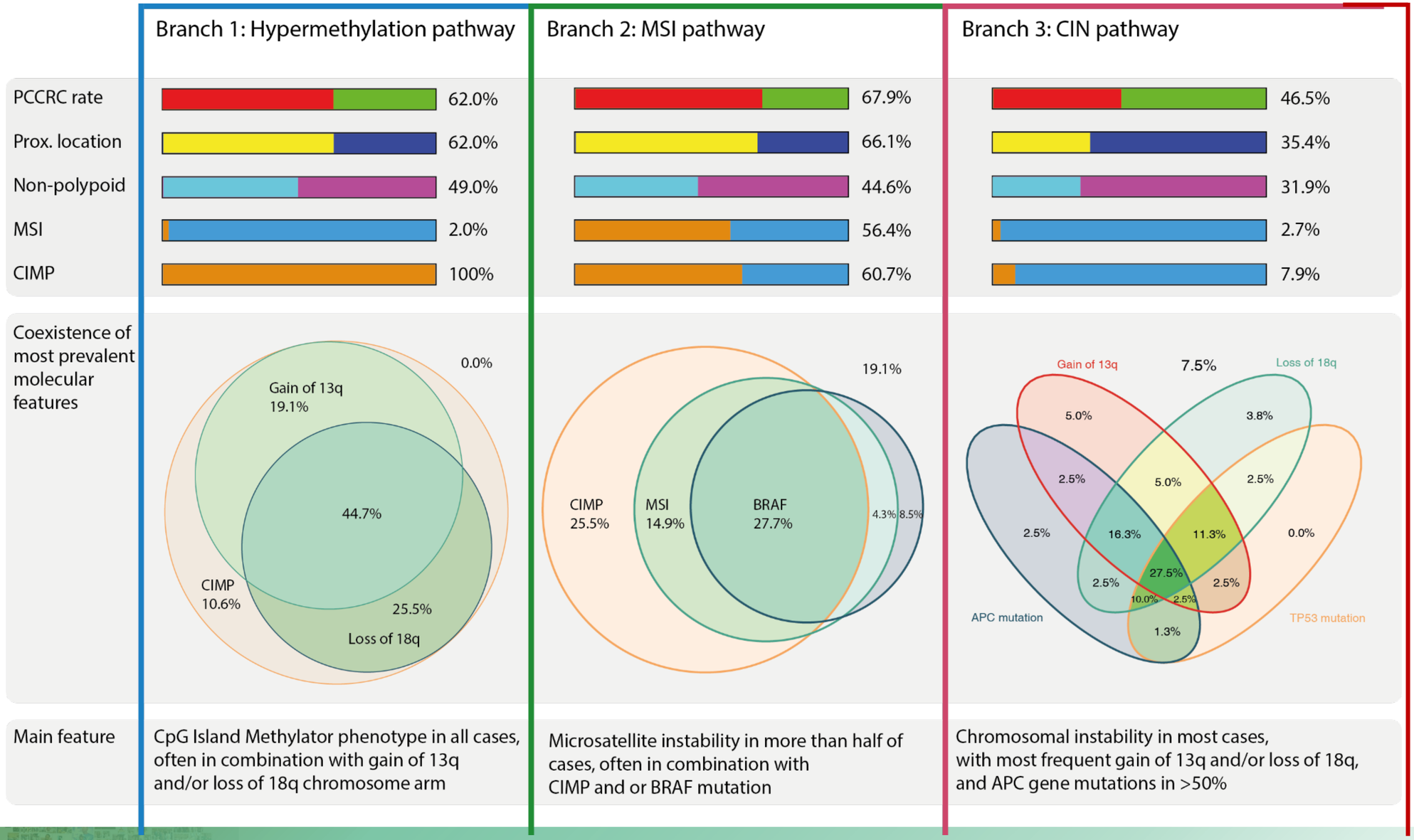
Corrected for age and gender

Results- PCCRCs are commonly CIMP-high

- Unsupervised hierarchial clustering
- Included molecular features:
  - Difference in univariate analysis of all PCCRC or biological PCCRC analyses
  - All mutations with observed prevalence of ≥9%
- Ward.D algorithm



Results- Overview



Bogie RMM ..Masclee AAM, Carvalho Bl BrJCancer 2022

Conclusions

- MSI, hypermethylation and CIN pathways play a role in the development of PCCRCs

- Key molecular features of PCCRCs:
  Less often 13q gain and 18q loss
  More often hypermethylated and MSI

- Similar molecular features in NP-CRNs and SSA/Ps → suggesting important contribution to PCCRCs

Discussion

- First comprehensive examination of the role of CIN- and MSI-associated mechanisms

Strengths

- Well characterized population-based collection of PCCRCs, nested case-control design
- Most likely etiologic factors identified

Limitations

- Retrospective
- Limited number of available tissue samples

Statement

The clinical and molecular features observed in PCCRCs support the hypothesis that SSLs and non-polypoid CRNs are contributors to the development of these cancers

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