Biomarkers in colorectal cancer

Pierre Laurent-Puig

Service de Médecine Génomique des tumeurs et cancers

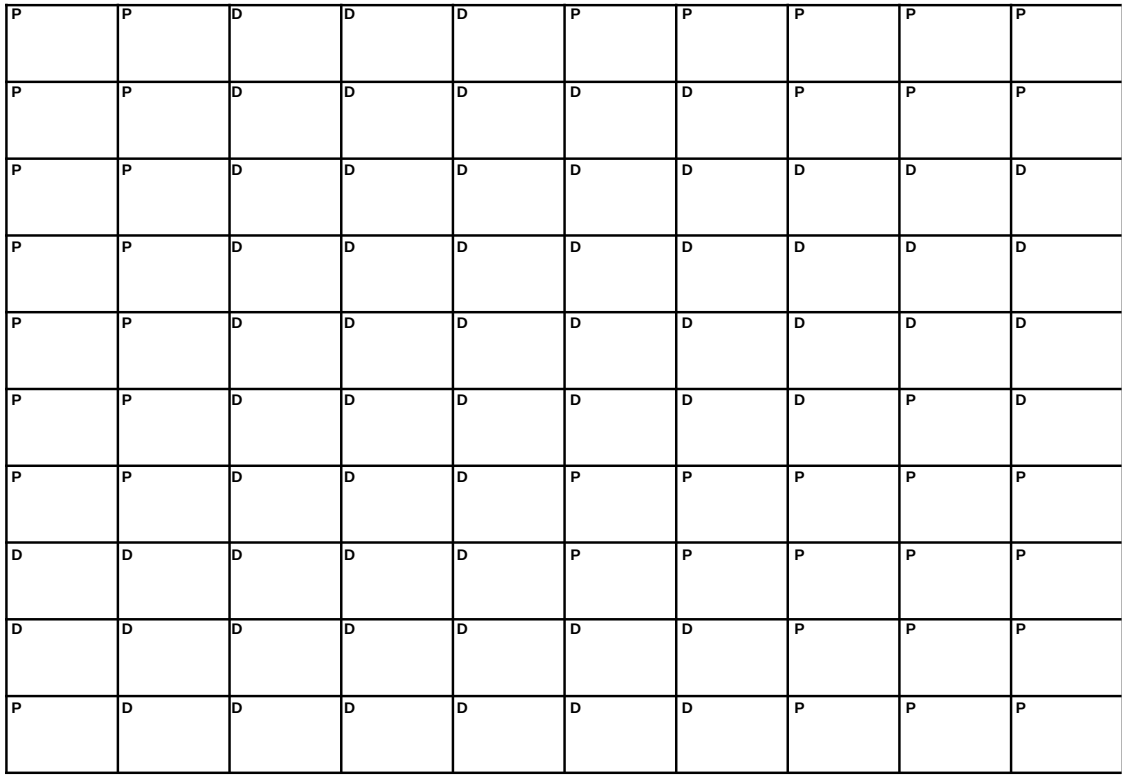
Hopital européen Georges Pompidou

Centre de recherche des Cordeliers

Colorectal Cancer Diversity

Diversity at the **genomic level**

At least **4 distinct entities**



D distal colon
P proximal colon

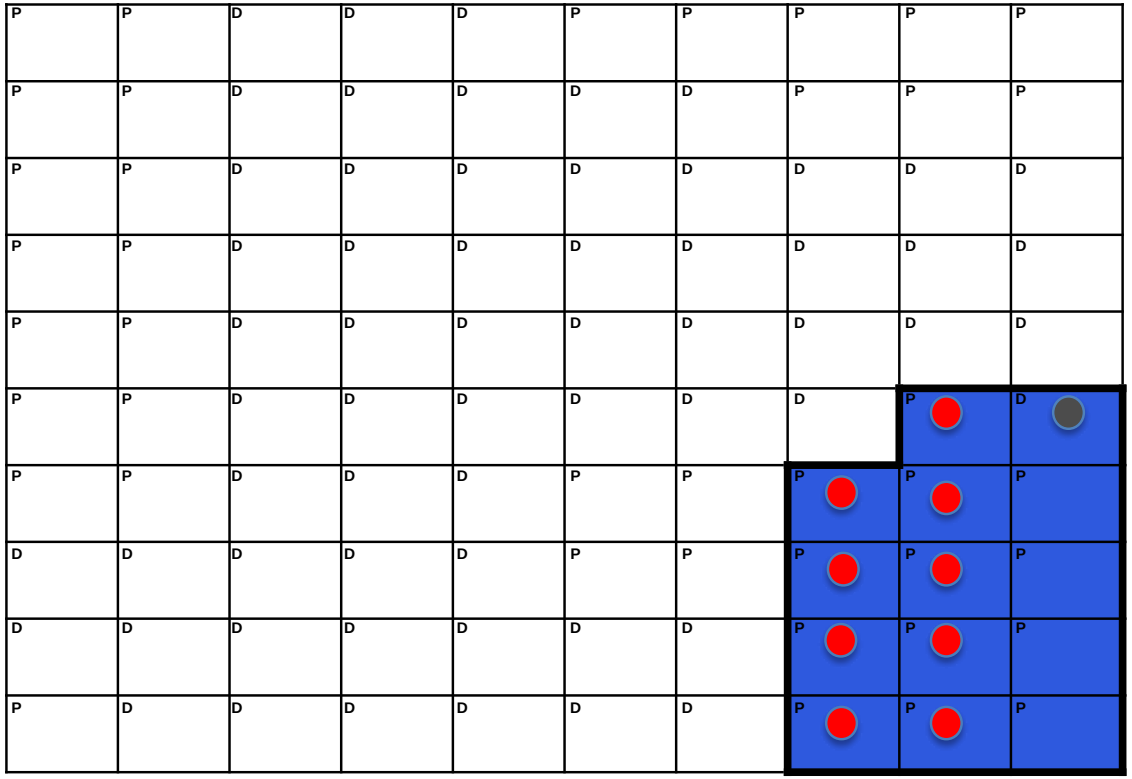
Barault et al. Cancer Res 2008;68:8541-46, Barault al. Int J cancer 2008;122:2255-59; & consortium colon CIT2

Colorectal Cancer Diversity

Diversity at the **genomic level**

At least **4 distinct entities**

- Microsatellite instable (MSI)



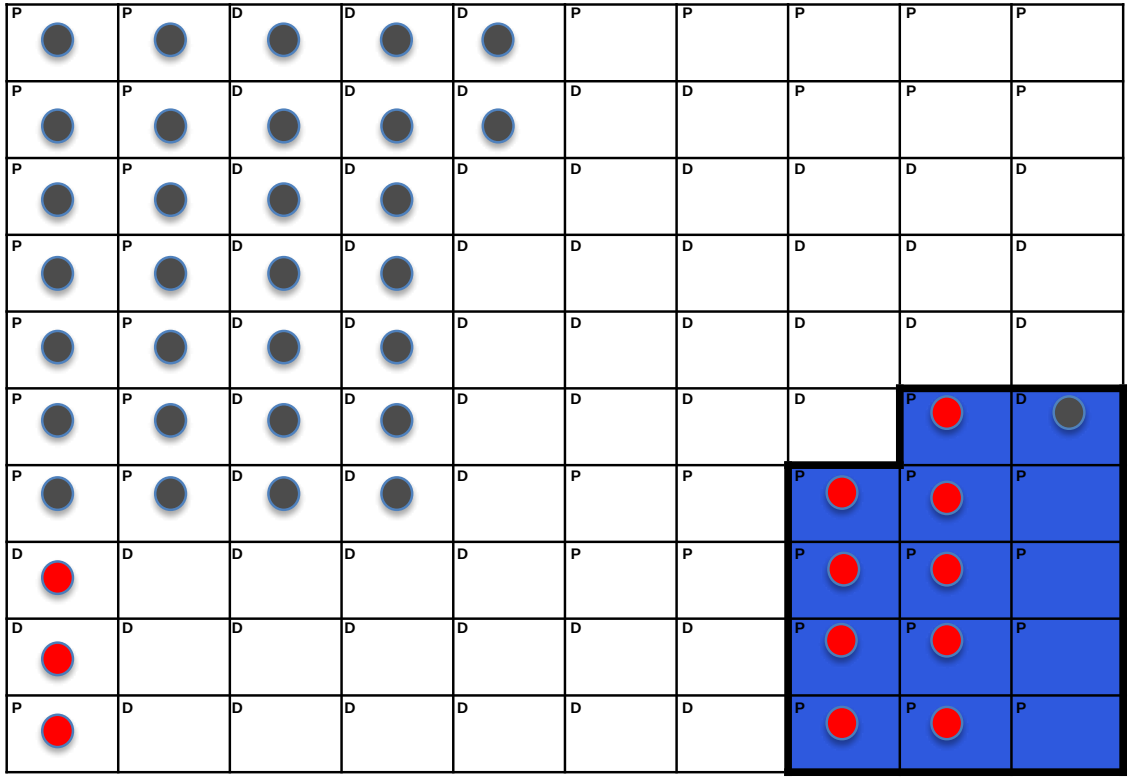
Barault et al. Cancer Res 2008;68:8541-46, Barault al. Int J cancer 2008;122:2255-59; & consortium colon CIT2

Colorectal Cancer Diversity

Diversity at the **genomic level**

At least **4 distinct entities**

- Microsatellite instable (MSI)
- Chromosomal instable (CIN)



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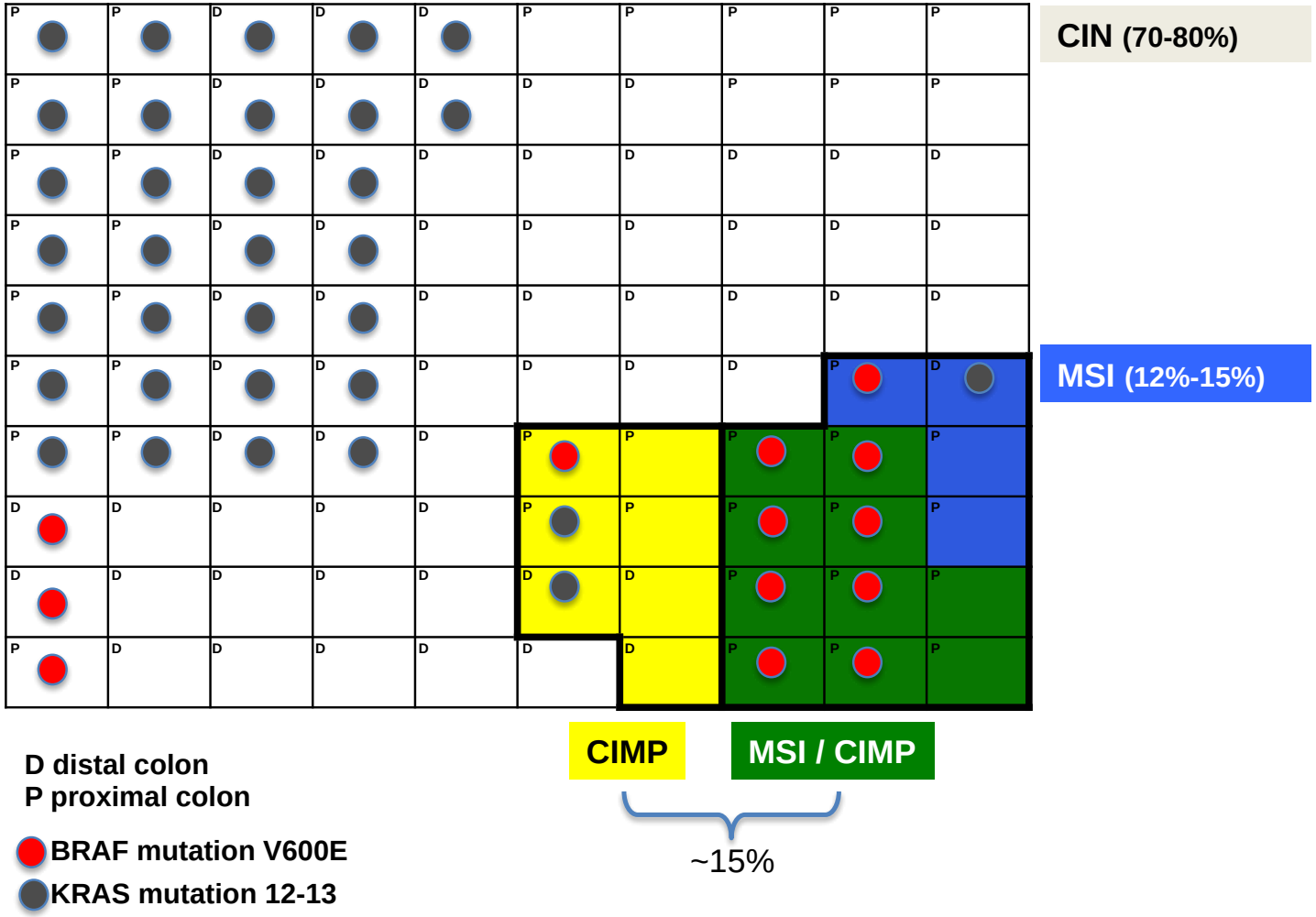
Colorectal Cancer Diversity

Diversity at the **genomic level**

At least **4 distinct entities**

- Microsatellite instable (MSI)
- Chromosomal instable (CIN)
- Hypermethylated (CIMP)



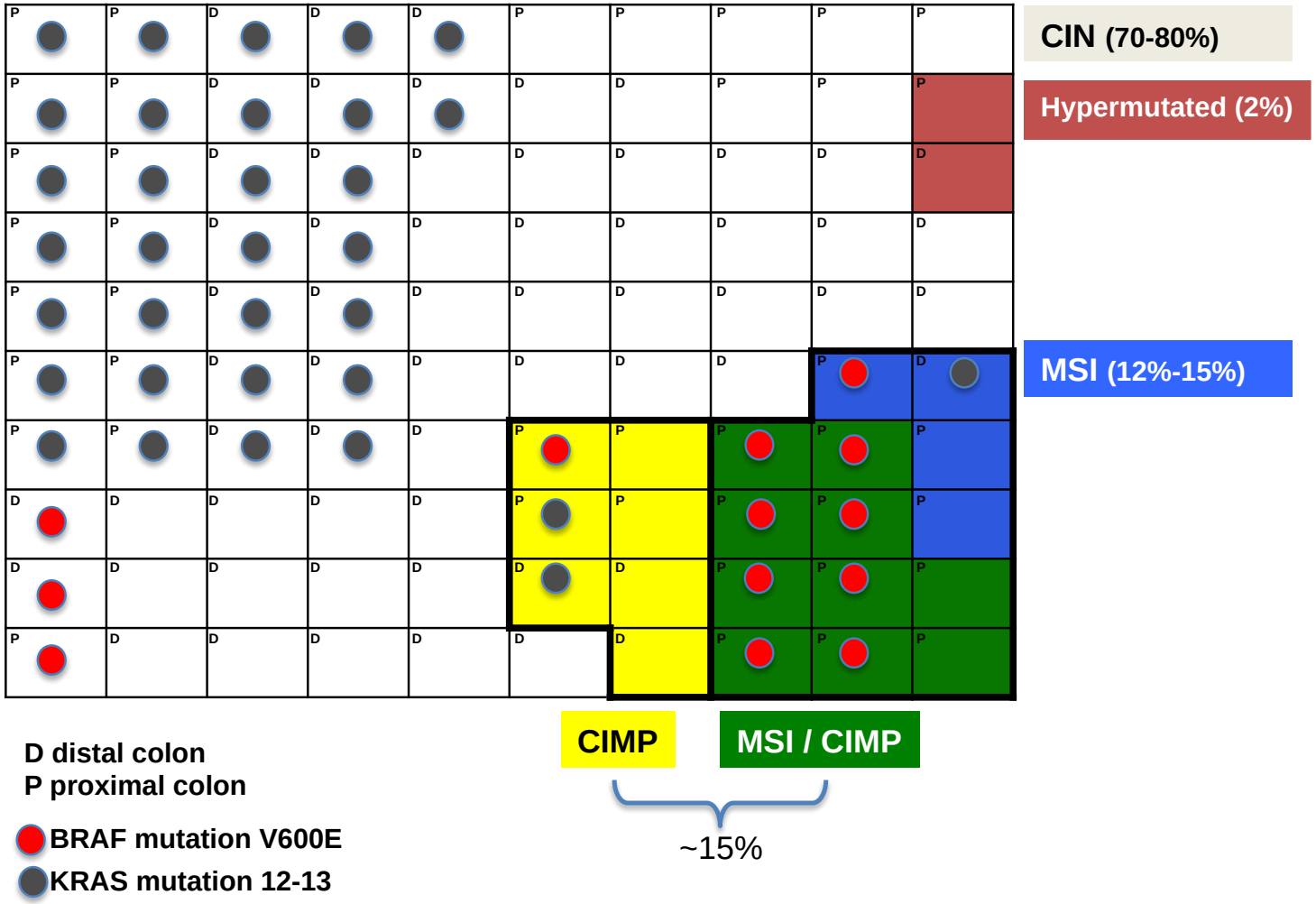
Barault et al. Cancer Res 2008;68:8541-46, Barault al. Int J cancer 2008;122:2255-59; & consortium colon CIT2

Colorectal Cancer Diversity

Diversity at the **genomic level**

At least **4 distinct entities**

- Microsatellite instable (MSI)
- Chromosomal instable (CIN)
- Hypermethylated (CIMP)
- Hypermutated



Barault et al. Cancer Res 2008;68:8541-46, Barault al. Int J cancer 2008;122:2255-59; & consortium colon CIT2

Colorectal Cancer Diversity

Diversity at the **gene expression level**

Distinct datasets / methods

6 publications

27 molecular subtypes

Marisa *et al. 2013* — 6 st

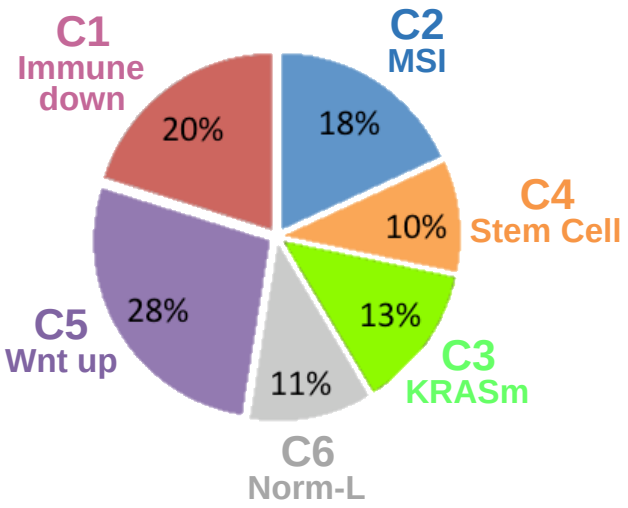
Budinska *et al. 2013* — 5 st

Roepman *et al. 2013* — 3 st

Sadanandam *et al. 2013* — 5 st

De Sousa *et al. 2013* — 3 st

Schlicker *et al. 2012* — 5 st



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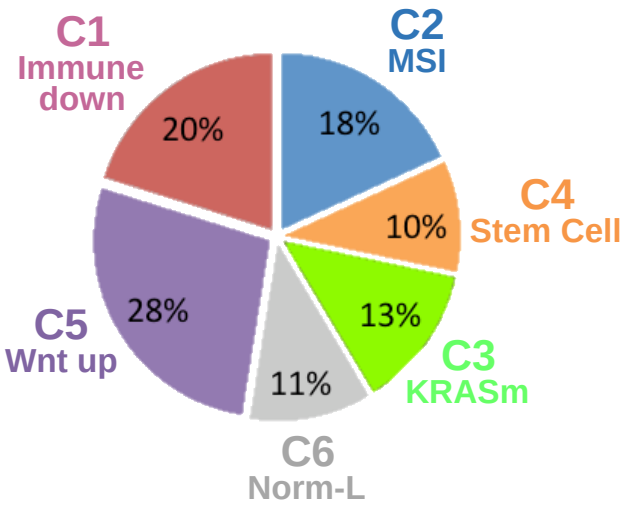
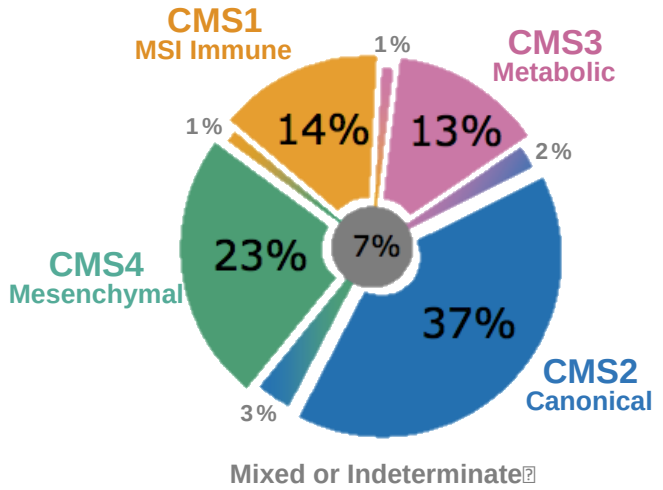
4 Consensus Subtypes

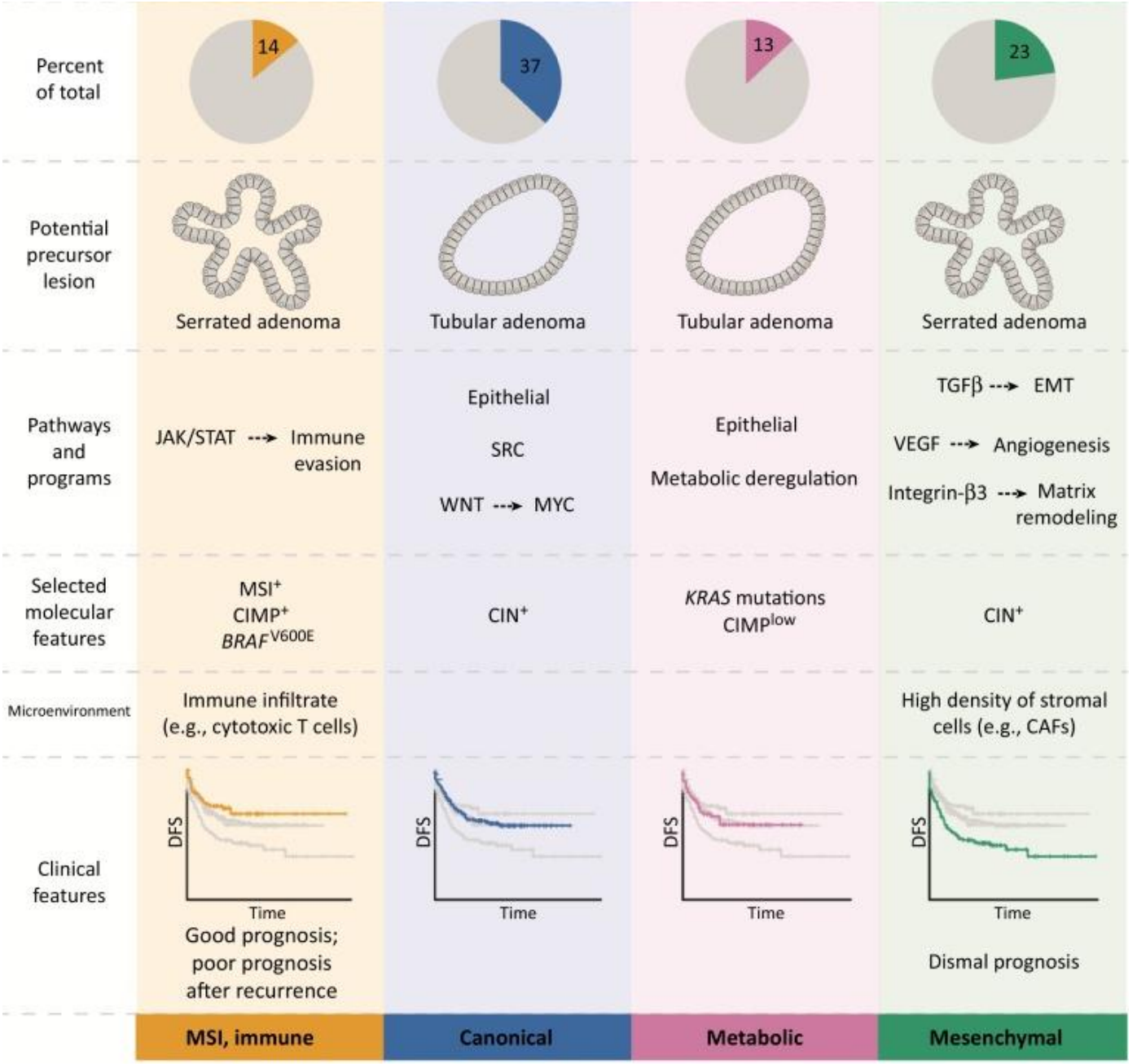
Guinney et al. 2015 (4 st) **CMS**





Colorectal Cancer Diversity

Transcriptomic classification of CRC: Inter tumor heterogeneity



Colorectal Cancer Diversity

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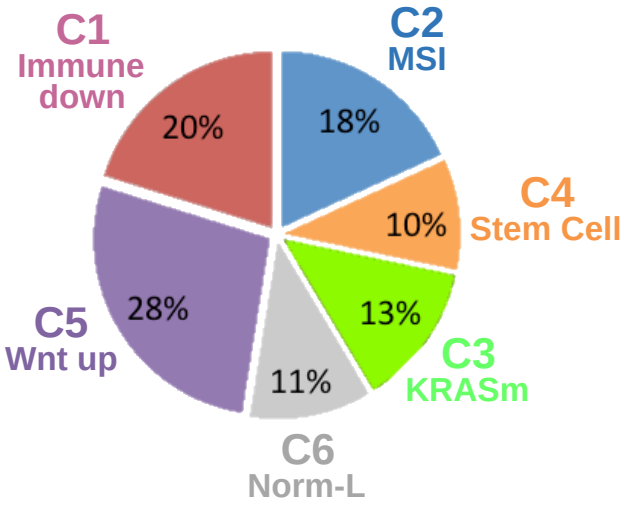
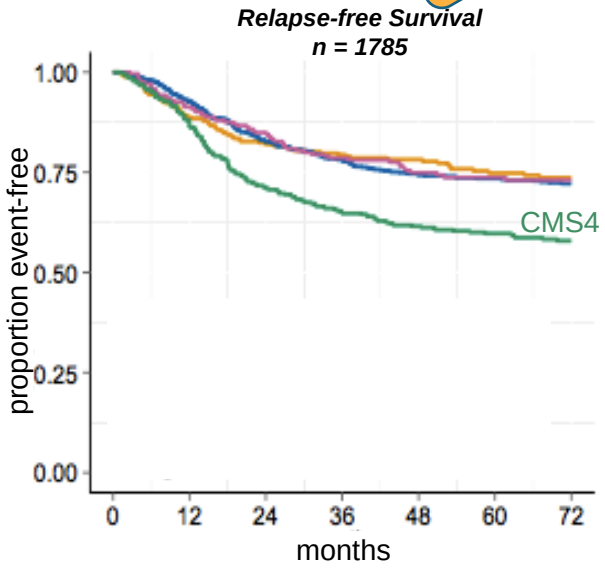
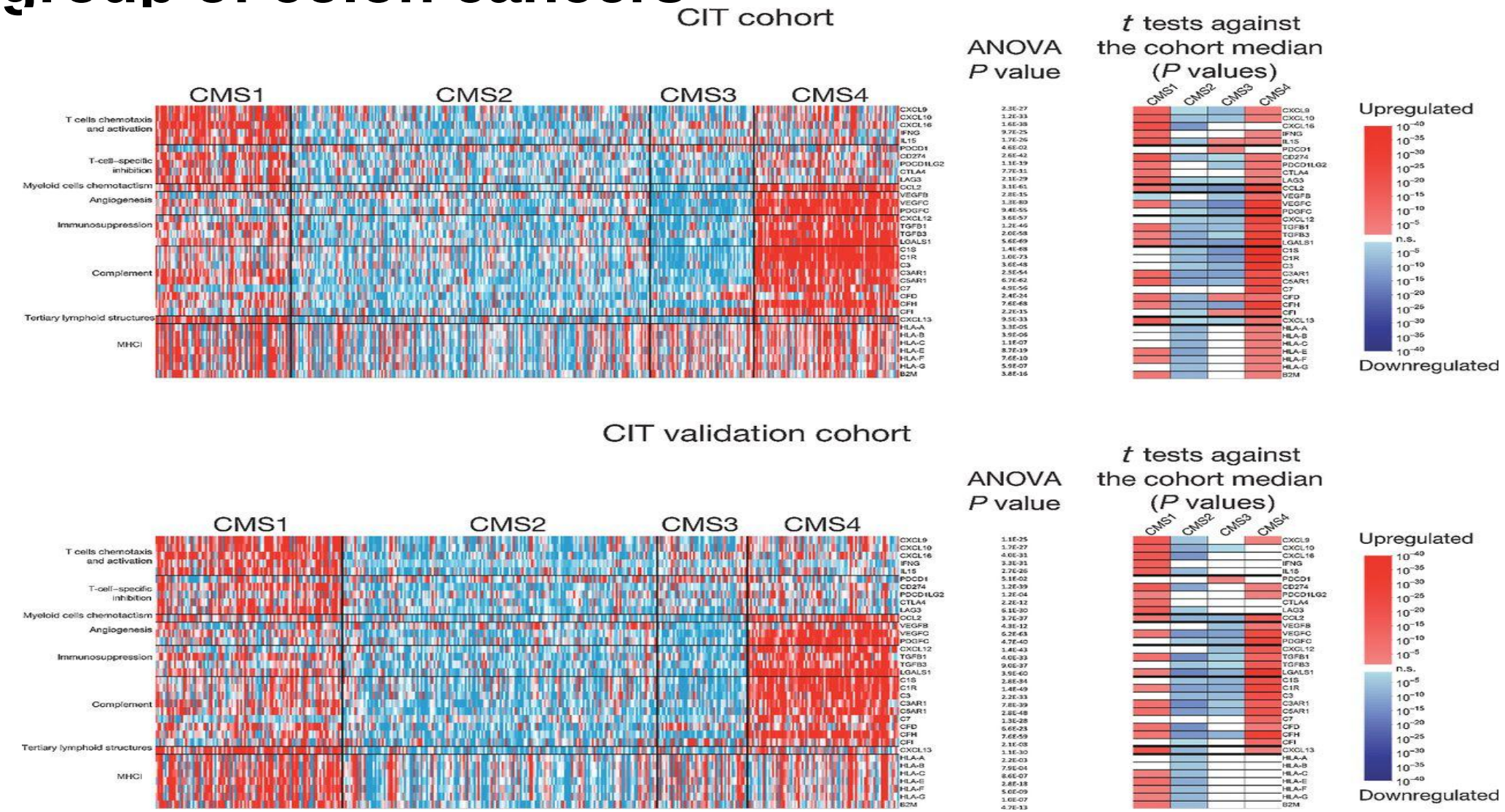


Can we refine this classification by integrating Immunology



Differentially expressed gene in the molecularly defined sub group of colon cancers



N=566

N=897

Becht et *al*, Clin Cancer Res 2016

Colorectal Cancer Diversity

Diversity at the **gene expression level**

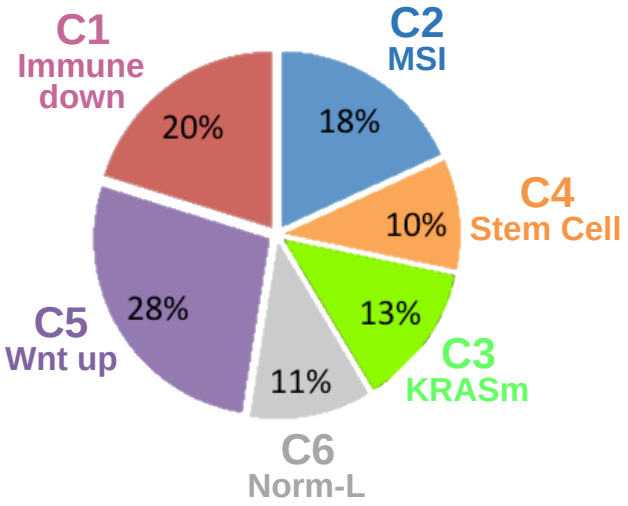
Distinct datasets / methods

6 publications **27 molecular subtypes**

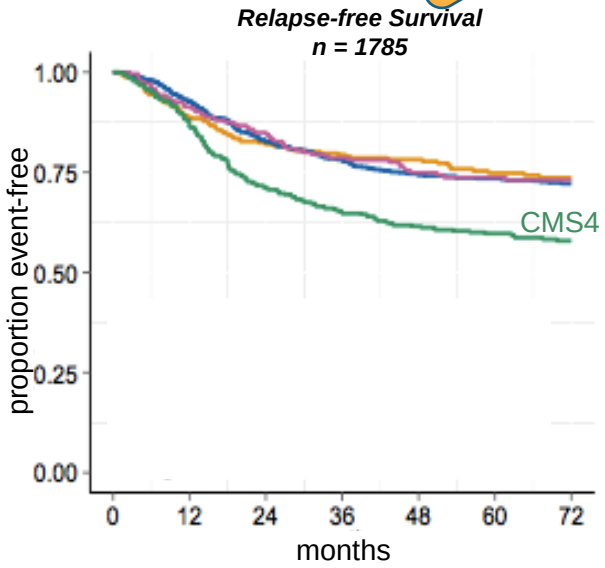
Marisa *et al. 2013* (6 st) | **Budinska** *et al. 2013* (5 st) | **Roepman** *et al. 2013* (3 st) | **Sadanandam** *et al. 2013* (5 st) | **De Sousa** *et al. 2013* (3 st) | **Schlicker** *et al. 2012* (5 st)

4 Consensus Subtypes

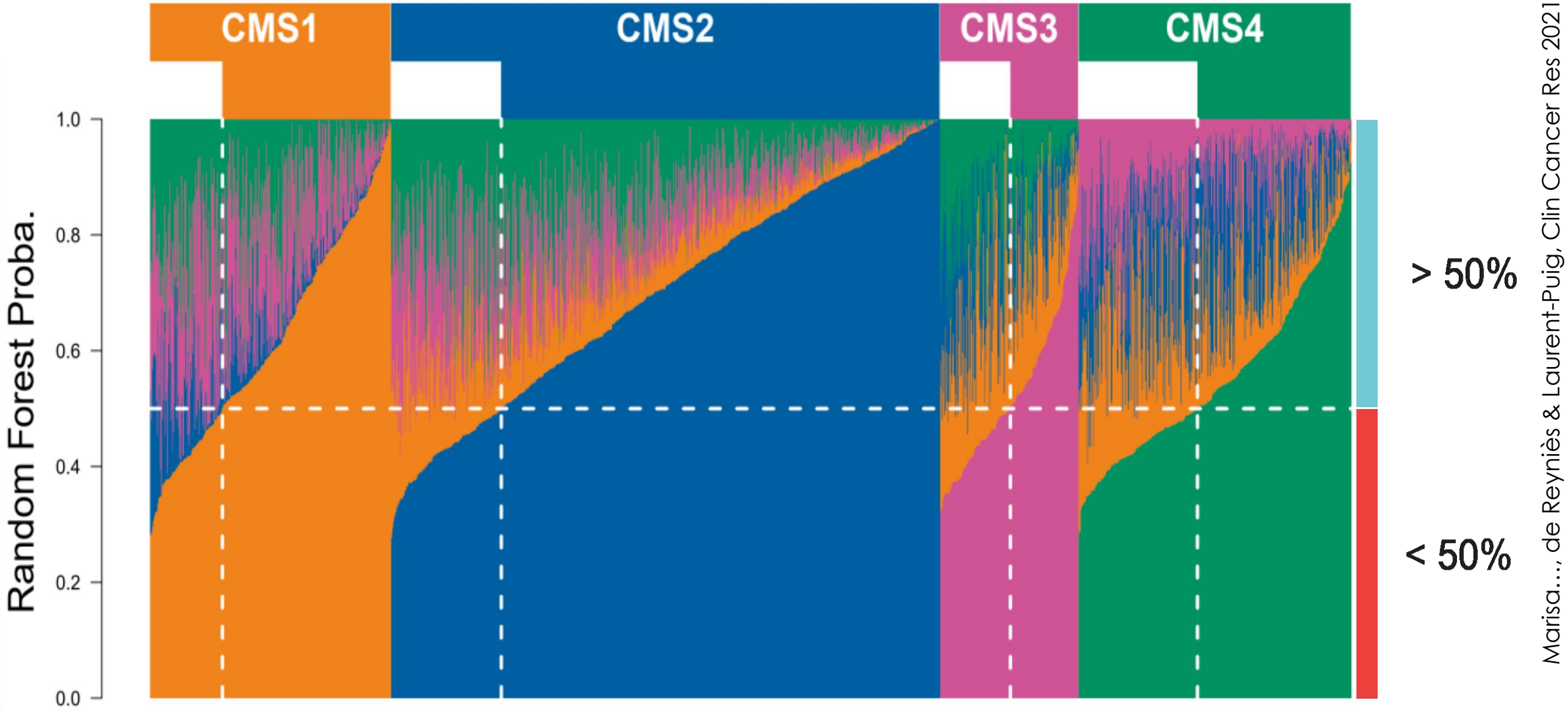
Guinney et al. 2015 (4 st) **CMS**



Can we refine this classification by dealing with heterogeneity



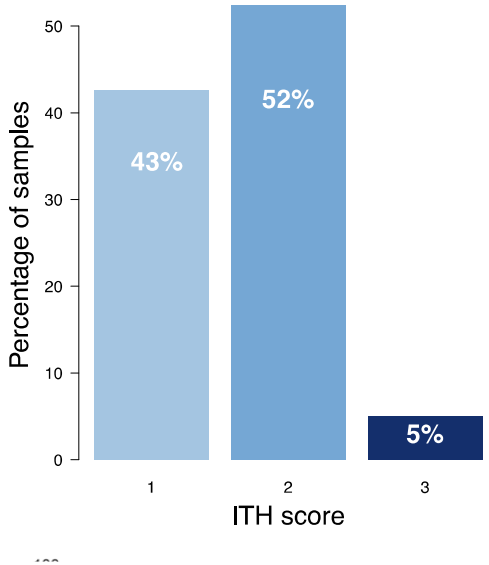
Transcriptomic classification of PETACC8 samples (stage III CRC):

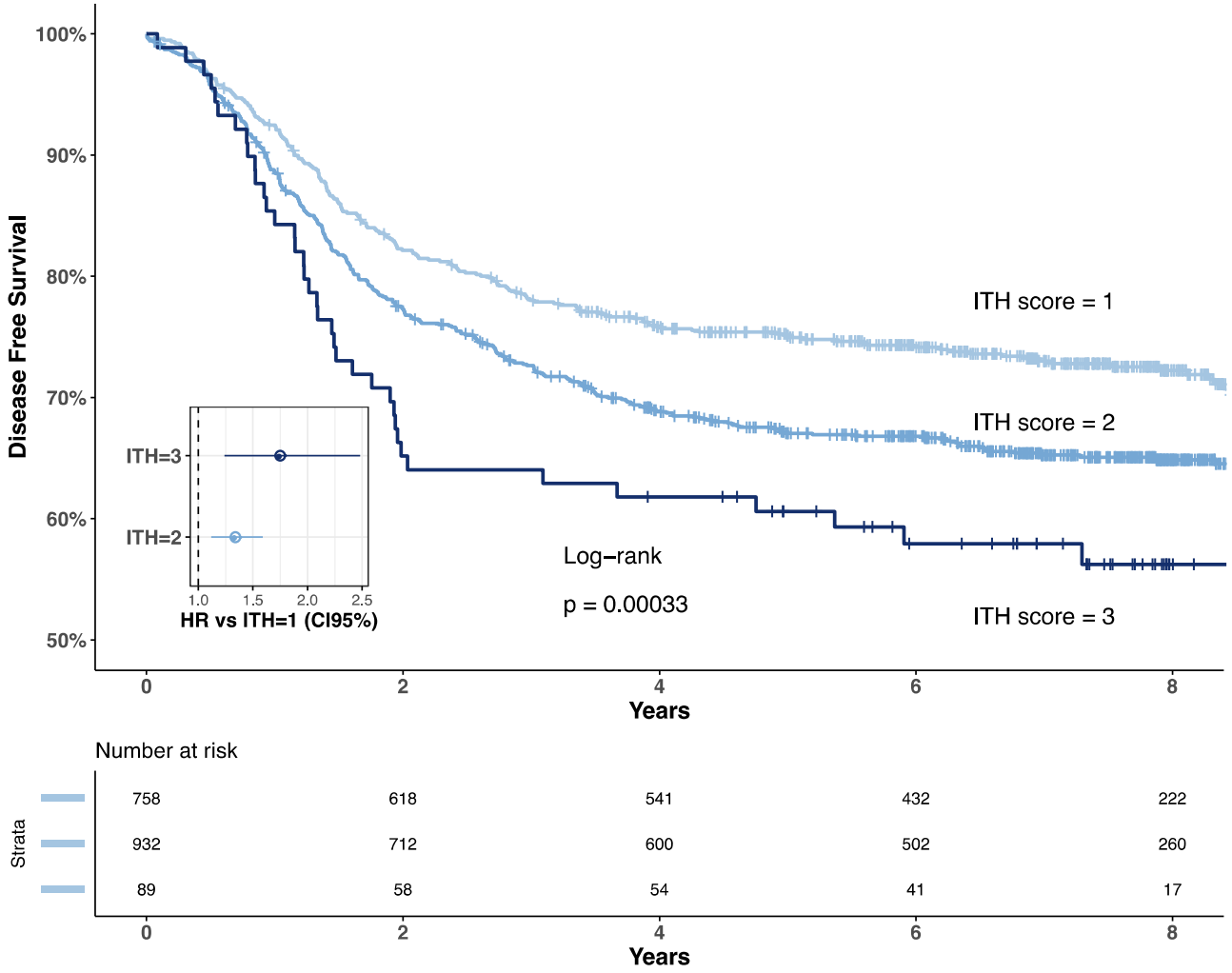


Marisa…, de Reyniès & Laurent-Puig, Clin Cancer Res 2021

➔ 31% samples with RF probability for CMS below 50%, suggesting intra-tumor heterogeneity

Transcriptomic classification of PETACC8 samples (stage III CRC): WISP (Weigthed in silico prediction) nanalysis





ITH score 2 or 3 ➔ worse prognosis (DFS, OS)

Marisa…, de Reyniès & Laurent-Puig, Clin Cancer Res 2021

Describe tumor heterogeneity

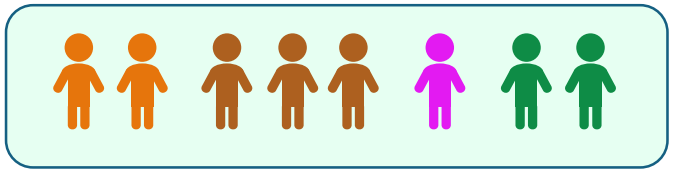
From the CRC consensus molecular classification to the identification of CMS heterogeneity

ANALYSIS

nature medicine

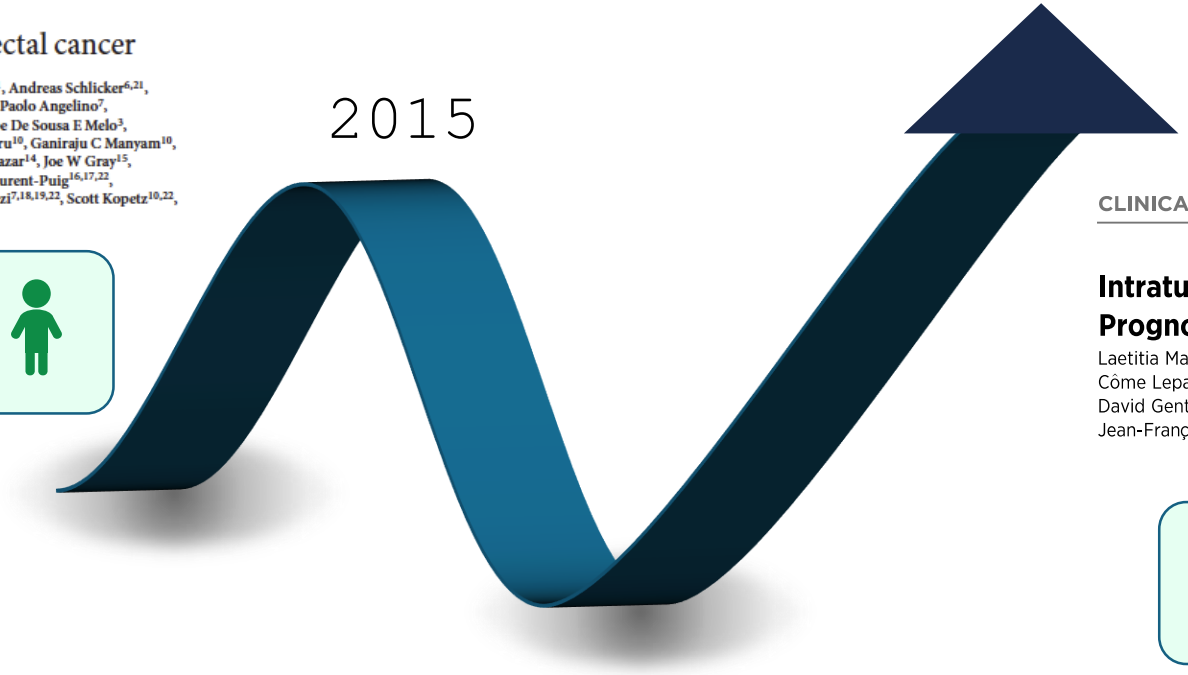
The consensus molecular subtypes of colorectal cancer

Justin Guinney[1,21], Rodrigo Dienstmann[1,2,21], Xin Wang[3,4,21], Aurélien de Reyniès[5,21], Andreas Schlicker[6,21], Charlotte Soneson[7,21], Laetitia Marisa[5,21], Paul Roepman[8,21], Gift Nyamundanda[9,21], Paolo Angelino[7], Brian M Bot[1], Jeffrey S Morris[10], Iris M Simon[8], Sarah Gerster[7], Evelyn Fessler[3], Felipe De Sousa E Melo[3], Edoardo Missiaglia[7], Hena Ramay[7], David Barras[7], Krisztian Homicsko[11], Dipen Maru[10], Ganiraju C Manyam[10], Bradley Broom[10], Valerie Boige[12], Beatriz Perez-Villamil[13], Ted Laderas[1], Ramon Salazar[14], Joe W Gray[15], Douglas Hanahan[11], Josep Tabernero[2], Rene Bernards[6], Stephen H Friend[1], Pierre Laurent-Puig[16,17,22], Jan Paul Medema[3,22], Anguraj Sadanandam[9,22], Lodewyk Wessels[6,22], Mauro Delorenzi[7,18,19,22], Scott Kopetz[10,22], Louis Vermeulen[3,22] & Sabine Tejpar[20,22]



2015

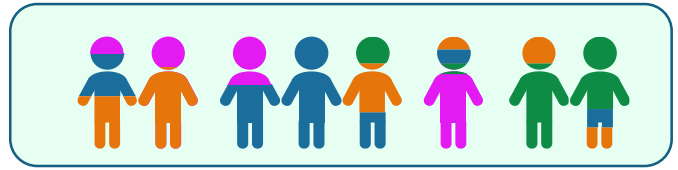
2021



CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Intratumor CMS Heterogeneity Impacts Patient Prognosis in Localized Colon Cancer

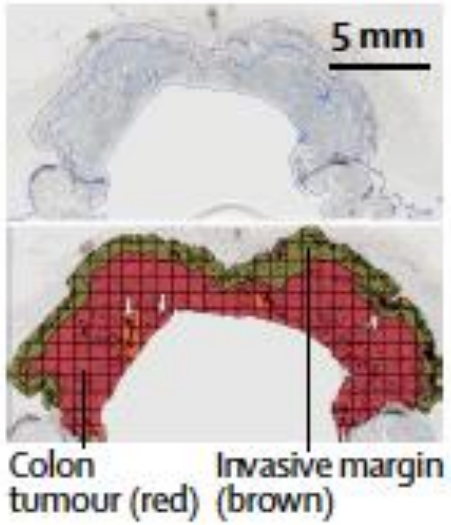
Laetitia Marisa[1], Yuna Blum[1], Julien Taieb[2,3], Mira Ayadi[1], Camilla Pilati[3], Karine Le Malicot[4], Côme Lepage[4,5], Ramon Salazar[6], Daniela Aust[7], Alex Duval[8], Hélène Blons[2,3], Valérie Taly[3], David Gentien[9], Audrey Rapinat[9], Janick Selves[10], Sophie Mouillet-Richard[3], Valérie Boige[3,11], Jean-François Emile[12], Aurélien de Reyniès[1], and Pierre Laurent-Puig[2,3]

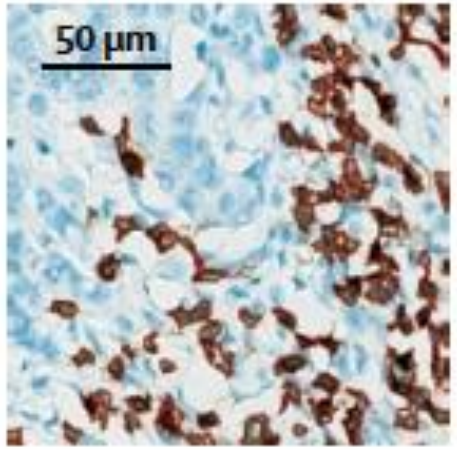


Prognostic biomarkers in localized CC

Immunoscore ®

= scoring system to summarise the **density of CD3+ and CD8+ T-cell** effectors within the **tumour** and its **invasive margin**

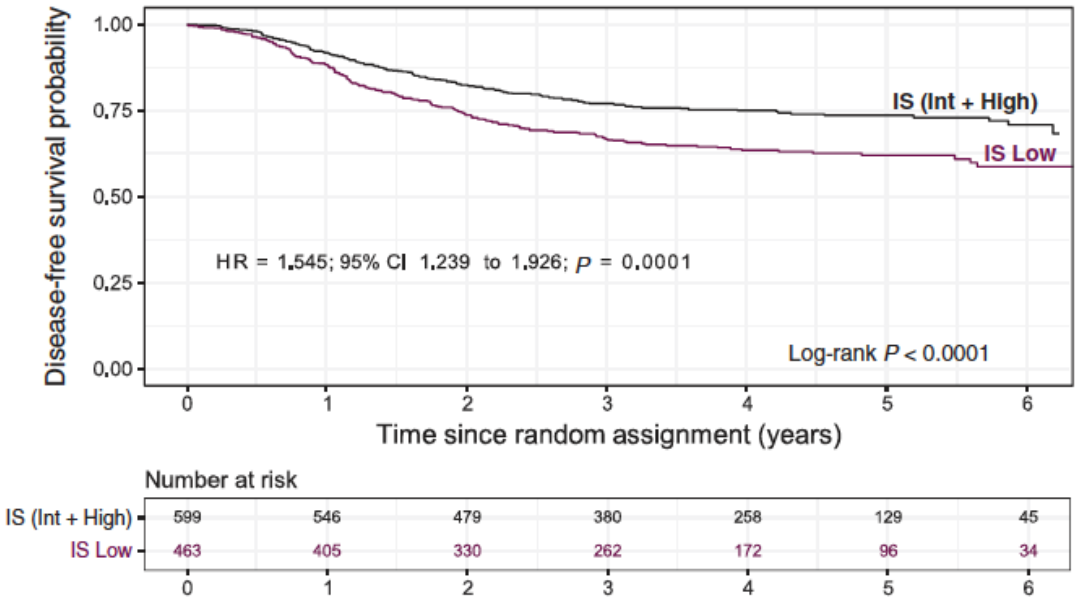




IHC of CD3+ cells

IDEA France trial

Stage III CC



Pagès et al. Lancet 2018

Pagès et al. Annals of Oncology 2020

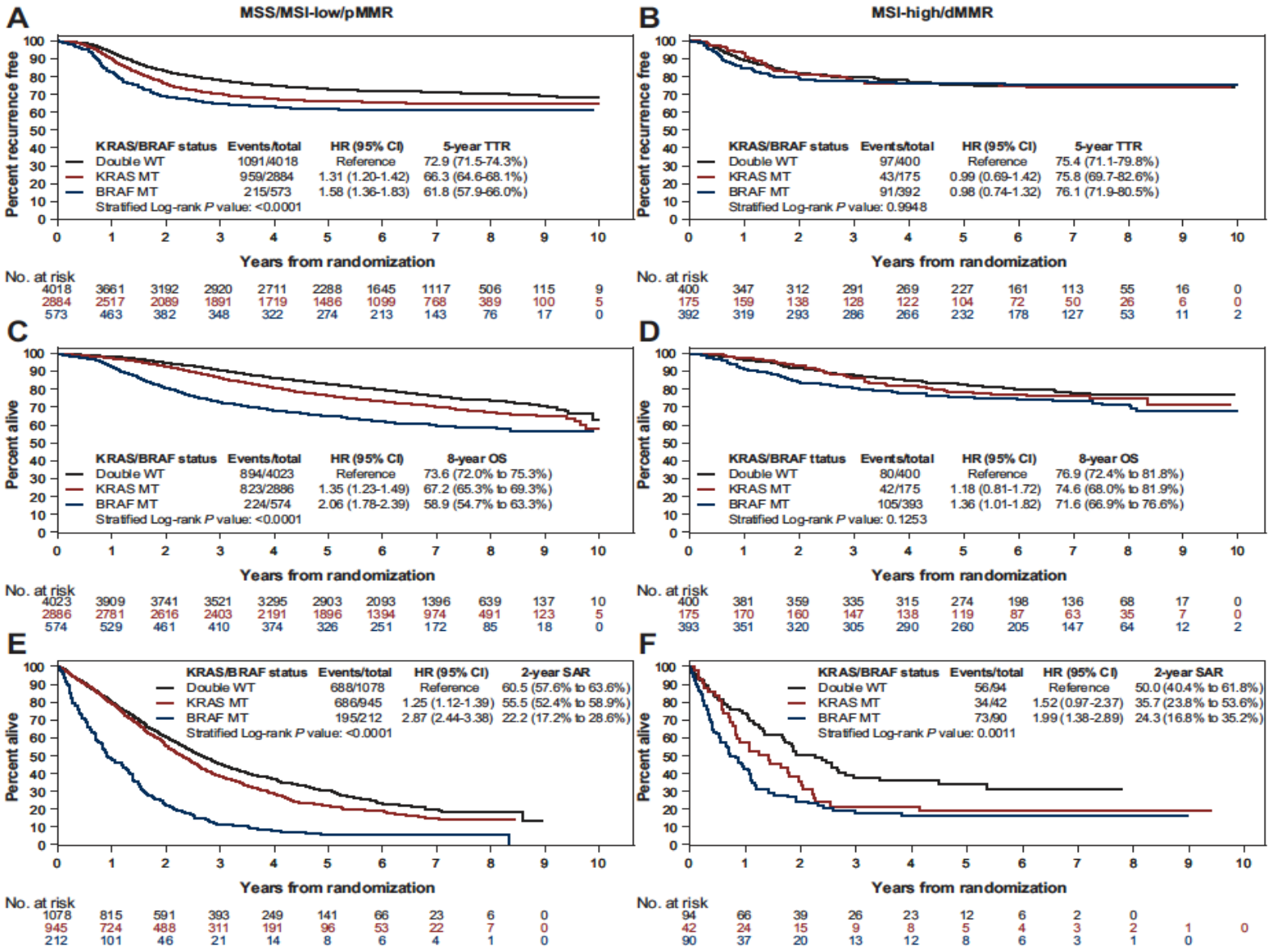
Prognostic biomarker in CCR stade III : *RAS/BRAF mutation*

Meta-analysis
ACCENT-IDEA database
N=8460 patients
Stage III CRC

SSM

SG

SAR



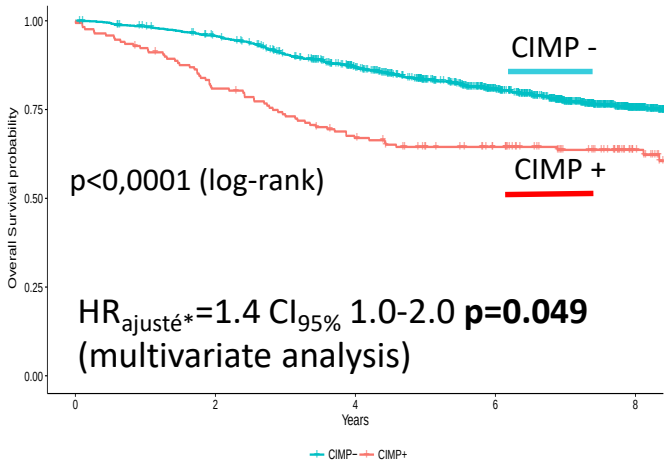
Taieb J et al. Annals of Oncol 2023

Prognostic biomarker in CCR stade III : CIMP+ phenotype

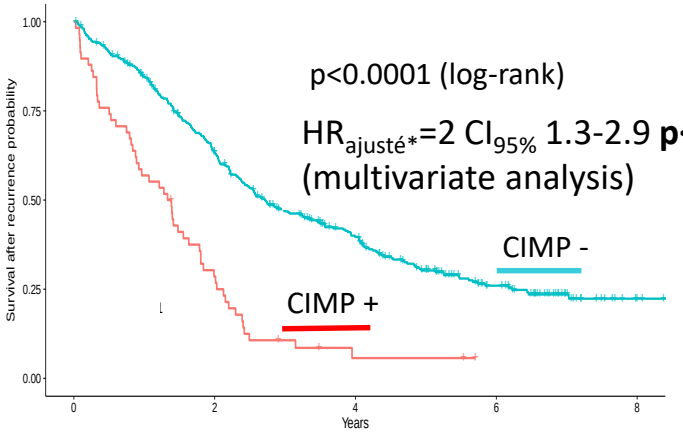
PETACC-8

MSS tumors (n=1560)

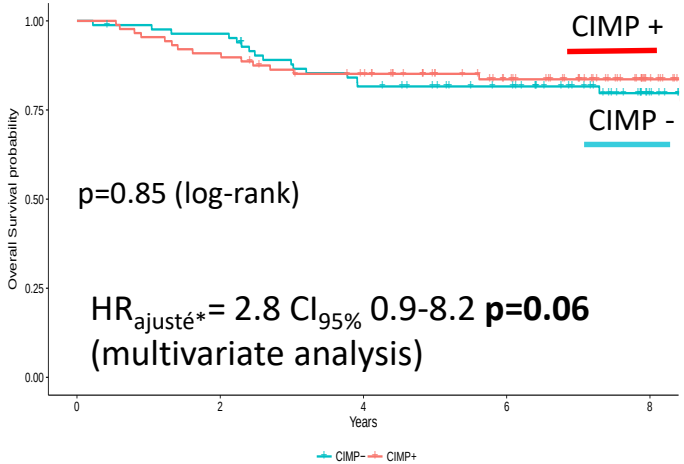
SG

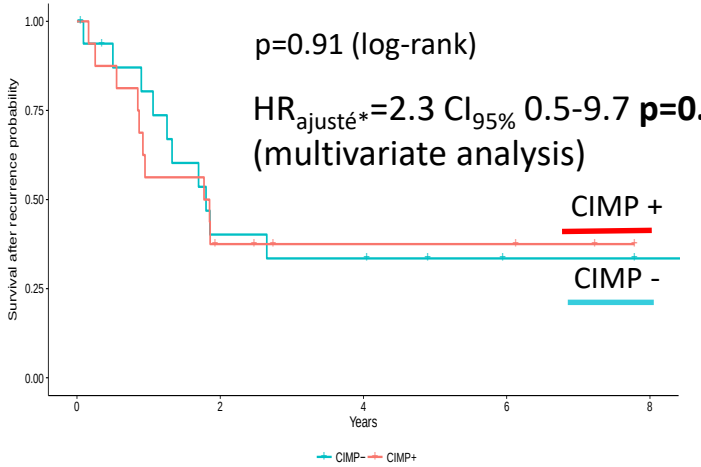


SAR



MSI tumors (n=172)





Poor prognostic value confirmed in the MSS/left colon subgroups and colon subgroups

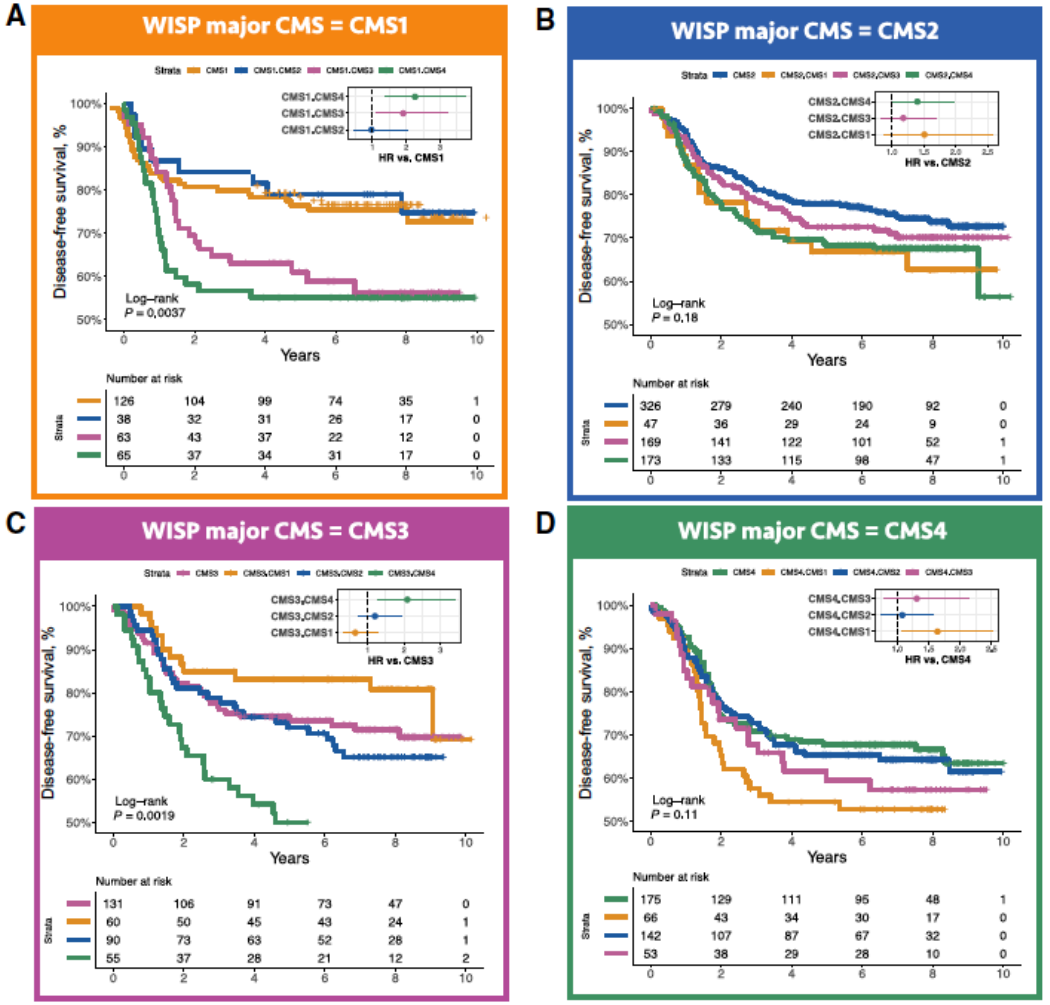
Gallois C et al. ESMO 2017
Gallois C et al. Clinical Cancer Research 2018

Prognostic biomarkers in localized CC

Intratumor CMS heterogeneity

PETACC-8 trial

Stage III CC

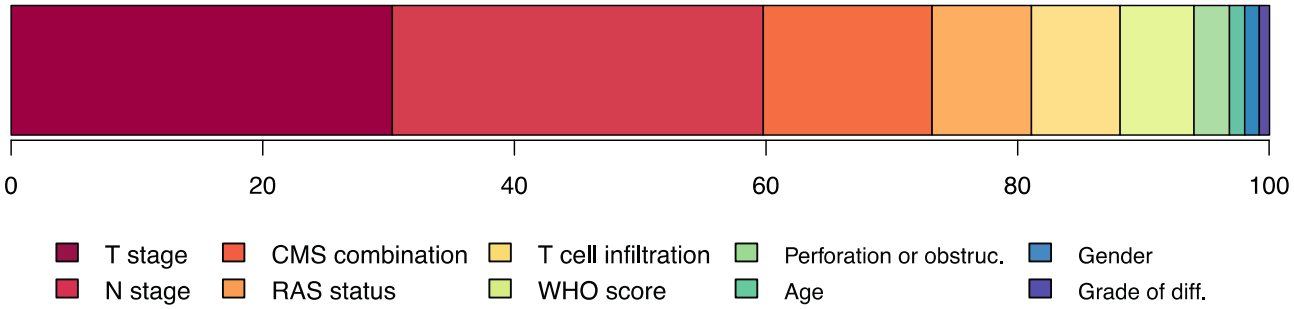


WISP deconvolution algorithm : for each sample → four CMS with different weights

- **Pure CMS**: 43% of samples
- **Mixed CMS** (CMS major . CMS minor)= 57% of samples

CMS combinations of poor prognosis:
CMS4.CMS1, CMS1.CMS4, CMS1.CMS3, CMS3.CMS4

Relative proportions of DFS explained variance in multivariate analysis



Marisa et al. Clin Cancer

Prognostic biomarker in CCR stade III : Oncotype DX Colon Cancer Recurrence Score®

7-gene panel associated with 3-year recurrence risk
Stage II-III CRC (surgery +/- FU/LV)"

RT-qPCR

Stromal	Cell cycle	Reference
BGN	*Ki-67*	*ATP5E*
FAP	*C-MYC*	*GPX1*
INHBA	*MYBL2*	*PGK1*
		UBB
		VDAC2

Early response
GADD45B

Recurrence Score (RS):

- Score stromal = (*BGN* + *FAP* + *INHBA*) ÷ 3
- Score cycle cellulaire = (*Ki-67* + *C-MYC* + *MYBL2*) ÷ 3

RS = 44 × ((+ 0.15 × score stromal − 0.30 × score cellulaire + 0.15 ×

Table 1. Prediction of Recurrence Risk: Kaplan-Meier Estimates of Recurrence Risk at 3 Years and Associated 95% CIs from Bootstrap Analysis for Patients With Stage II Disease in Surgery-Alone Studies

Recurrence Risk Group	Patients (median %)	Risk of Recurrence at 3 Years (%)	95% CI
Low (RS < 30)	25	8	5 to 12
Intermediate (RS 31-40)	39	11	7 to 15
High (RS ≥ 41)	37	25	18 to 32

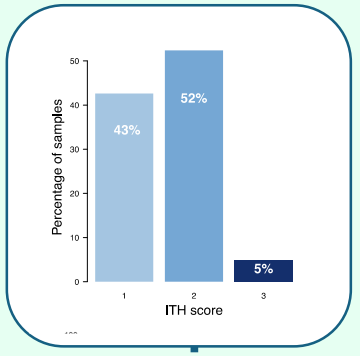
Abbreviation: RS, recurrence score.

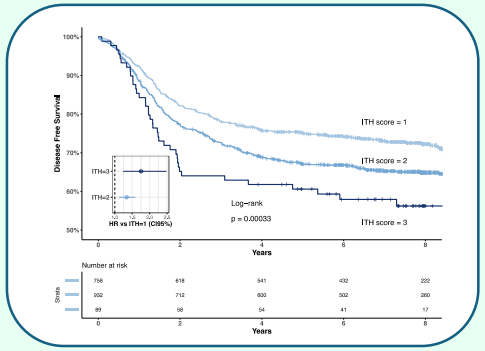
O'Connell et al. JCO

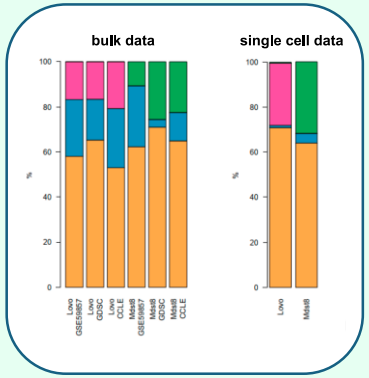
Uncovering tumor heterogeneity

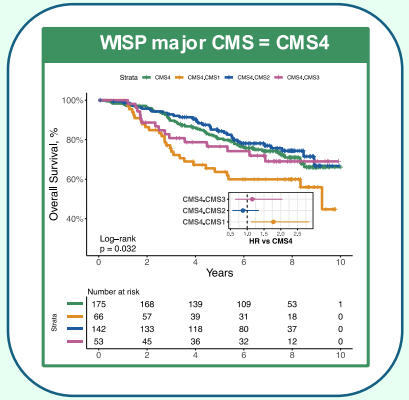
Key findings:

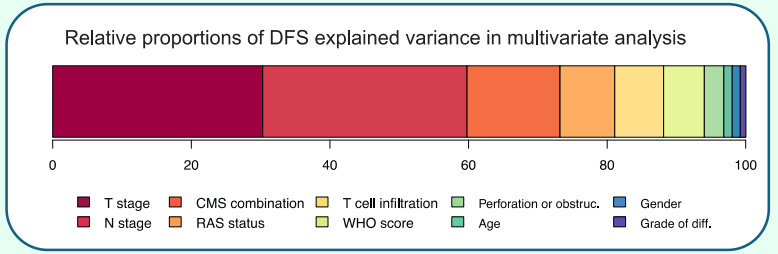
- ITH is frequent
- ITH is associated with poor prognosis
- ITH is recovered in cell lines
- Some CMS combinations are particularly unfavorable
- CMS combinations improve the prognostication of patients









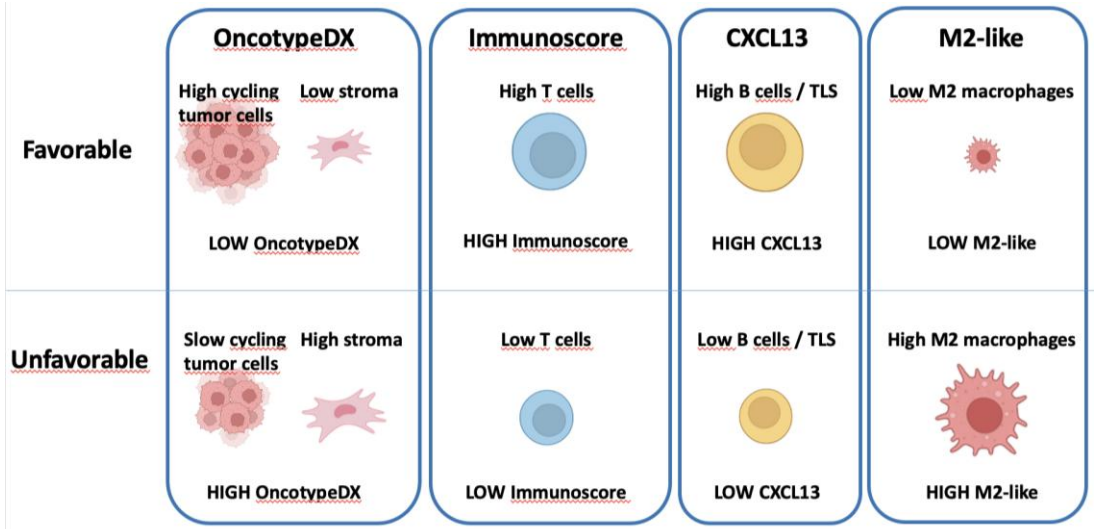


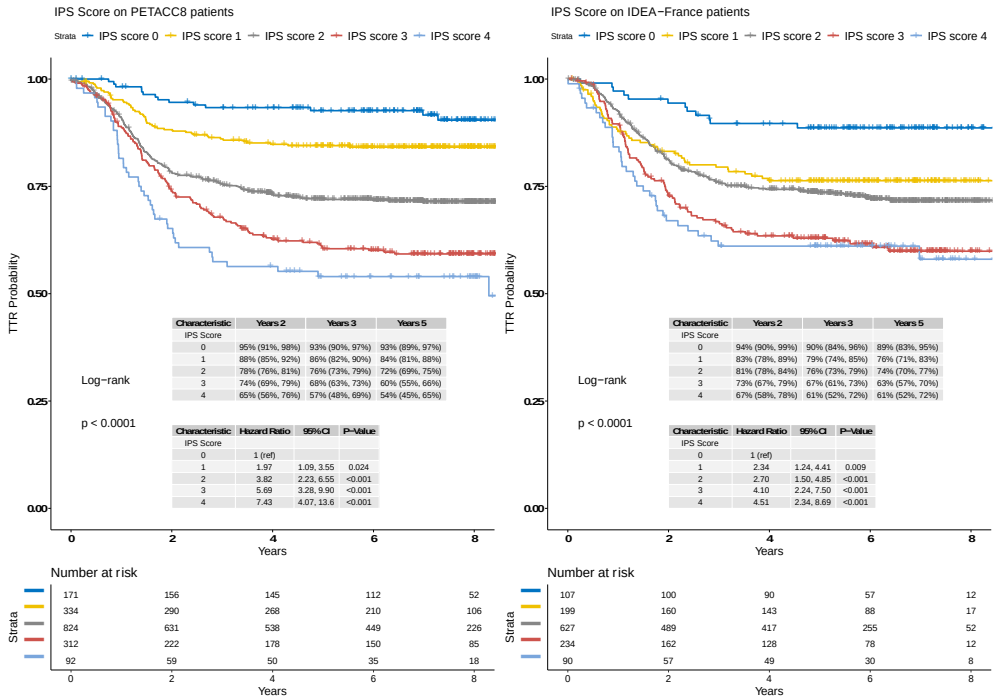
Marisa et al., Clin. Cancer Res 2021

Transcriptomic signatures can improve patient stratification in CRC

Key findings :

- Transcriptomic signatures of the tumor microenvironment and cell cycle can predict recurrence in stage III colon cancer from PETACC-8 and IDEA France trials





Gallois et al. J Clin Oncol 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO GASTROINTESTINAL ONCOLOGY

ORIGINAL ARTICLE

Genetic and transcriptomic analyses of early-onset colon cancer (EOCC): a *post hoc* analysis of 2973 patients from two adjuvant randomized trials

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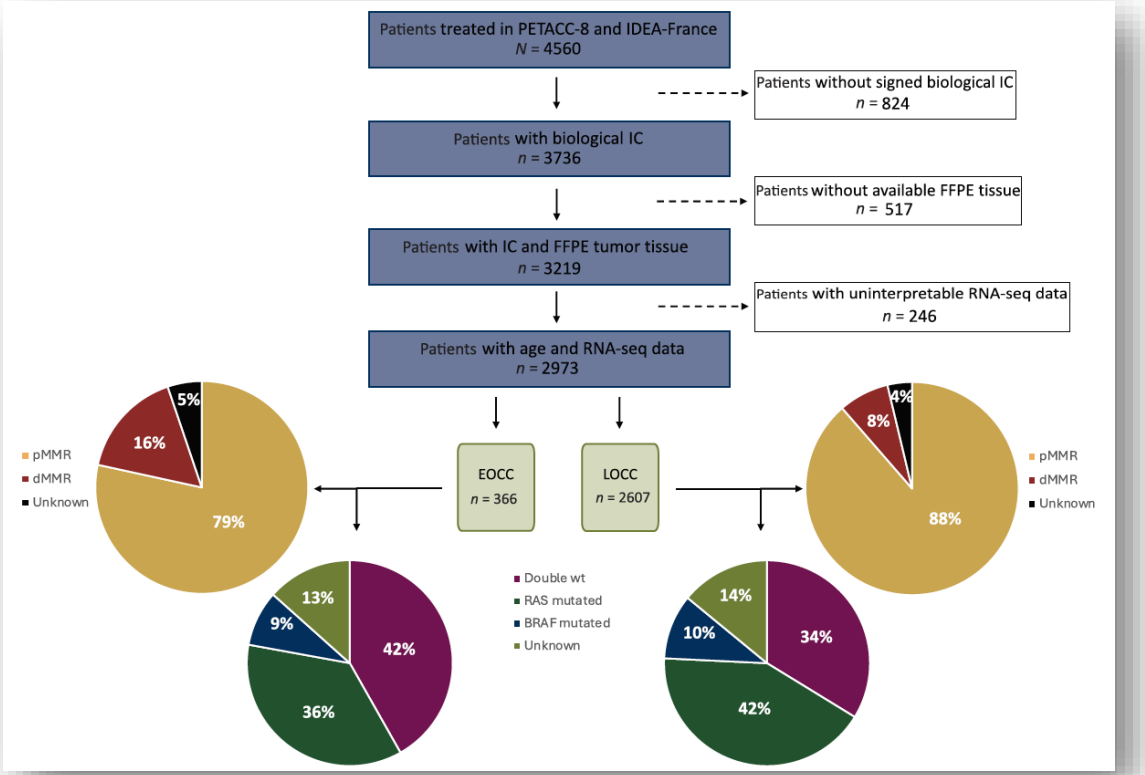


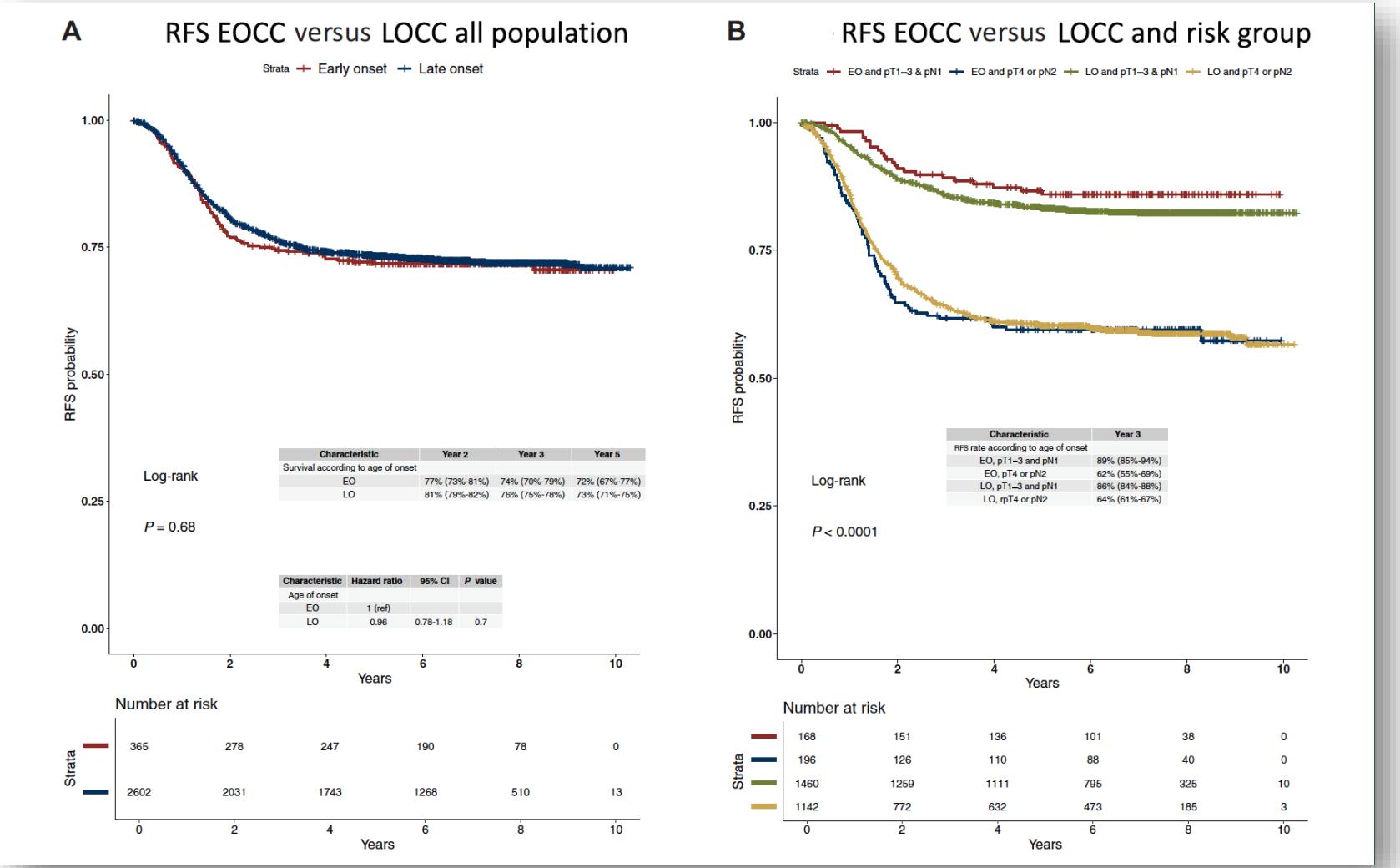
Mutation frequency according to age at onset

Table 2. Extensive genetic profiling of patients in PETACC-8, IDEA-France, and in the pooled analysis of both

	All population			pMMR			dMMR		
	EO $n = 366$	LO $n = 2607$	*P* value[a]	EO $n = 287$	LO $n = 2310$	*P* value[a]	EO $n = 60$	LO $n = 200$	*P* value[a]
KRAS, *n* (%)			**0.044**			**0.022**			**0.002**
M	123 (39)	1006 (45)		101 (40)	946 (47)		21 (40)	35 (19)	
NM	194 (61)	1240 (55)		153 (60)	1052 (53)		32 (60)	148 (81)	
NA	49	361		33	312		7	17	
BRAF, *n* (%)			0.3			0.3			**<0.001**
M	32 (10)	266 (12)		26 (10)	167 (8.4)		6 (11)	91 (50)	
NM	286 (90)	1975 (88)		229 (90)	1827 (92)		47 (89)	92 (50)	
NA	48	366		32	316		7	17	
PTEN, *n* (%)			**<0.001**			**0.003**			0.3
M	27 (8.5)	85 (3.8)		14 (5.5)	46 (2.3)		12 (23)	31 (17)	
NM	290 (91)	2156 (96)		240 (94)	1948 (98)		41 (77)	152 (83)	
NA	49	366		33	316		7	17	
CTNNB1, *n* (%)			**<0.001**			0.067			0.3
M	20 (6.3)	56 (2.5)		8 (3.1)	30 (1.5)		9 (17)	21 (11)	
NM	297 (94)	2186 (98)		246 (97)	1964 (98)		44 (83)	162 (89)	
NA	49	365		33	316		7	17	

Gandini et al. EMSO Gastrointestinal Oncology, Volume 7, 100106

Prognosis of patients according to age at onset and risk groups



Gandini et al. EMSO Gastrointestinal Oncology, Volume 7, 100106

CMS distribution according to age

Table 3. **CMS distribution according to age group**

CMS	PETACC-8			IDEA-France			Total			Total dMMR			Total pMMR		
	EO, *n* (%) *n* = 275	LO, *n* (%) *n* = 1458	*P* value[a]	EO, *n* (%) *n* = 93	LO, *n* (%) *n* = 1159	*P* value[a]	EO, *n* (%) *n* = 368	LO, *n* (%) *n* = 2617	*P* value[a]	EO, *n* (%) *n* = 60	LO, *n* (%) *n* = 201	*P* value[a]	EO, *n* (%) *n* = 289	LO, *n* (%) *n* = 2317	*P* value[a]
1	67 (25)	242 (17)	**0.012**	21 (23)	157 (14)	**0.045**	88 (24)	399 (15)	**<0.001**	43 (74)	143 (72)	0.9	40 (14)	239 (10)	0.2
2	88 (33)	547 (38)		22 (24)	397 (35)		110 (30)	944 (36)		1 (1.7)	5 (2.5)		107 (37)	915 (40)	
3	50 (19)	312 (22)		21 (23)	244 (21)		71 (20)	556 (21)		11 (19)	34 (17)		55 (19)	508 (22)	
4	65 (24)	347 (24)		27 (30)	351 (31)		92 (25)	698 (27)		3 (5.2)	18 (9)		85 (30)	645 (28)	
NA	5	10		0	0		5	10		2	0		2	10	

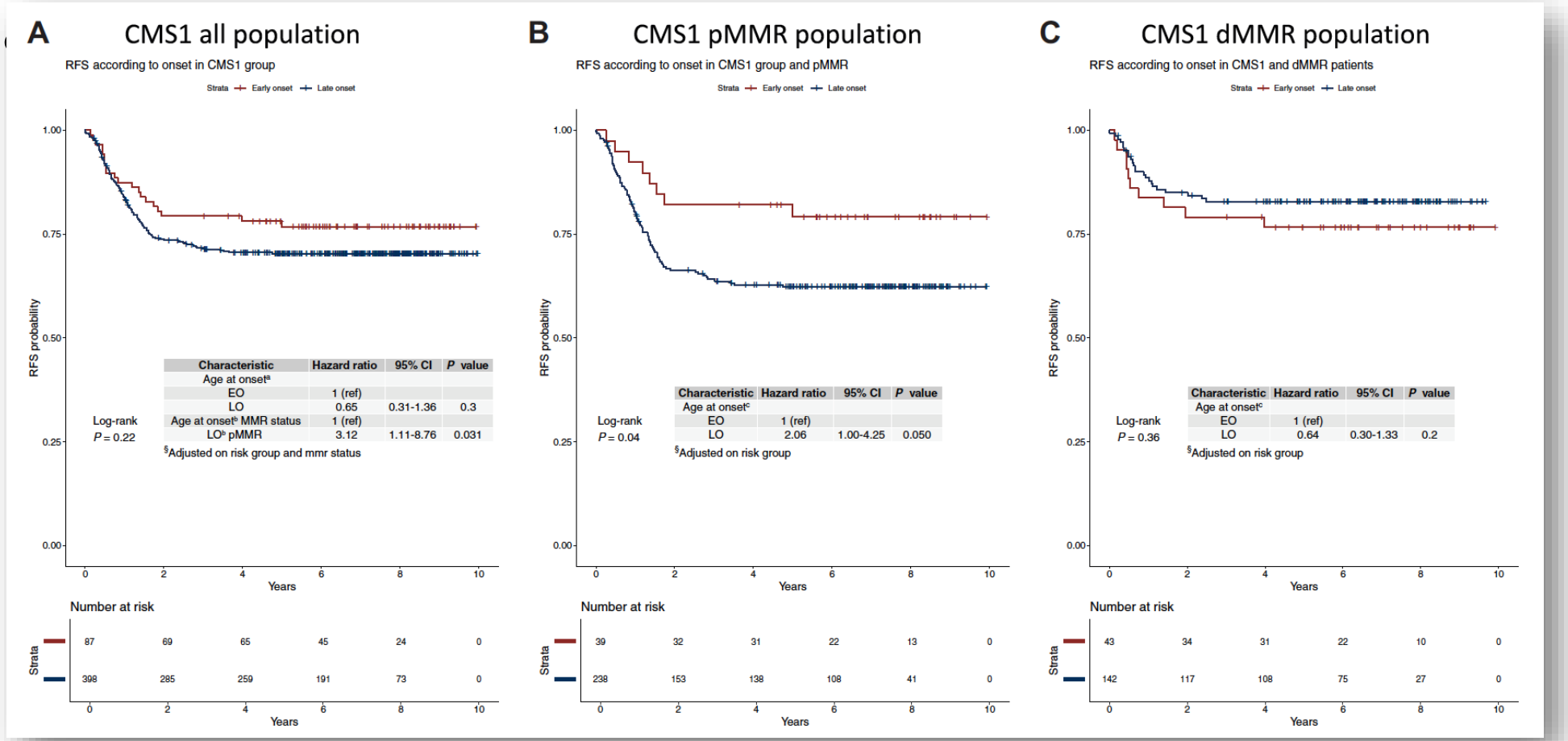
Statistically significant *P*-values are highlighted in bold.

CMS, consensus molecular subtypes; dMMR, mismatch repair deficiency; EO, early onset; LO, late onset; NA, not available; pMMR, mismatch repair proficiency.

[a]Pearson's chi-square test; Fisher's exact test.

Gandini et al. EMSO Gastrointestinal Oncology, Volume 7, 100106

Interaction between age at onset and MMR status for prognostication of CMS1 colon C



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