Characterization of atypical dMMR (deficient MisMatch Repair) tumors: a study from a large cohort of 4948 cases.

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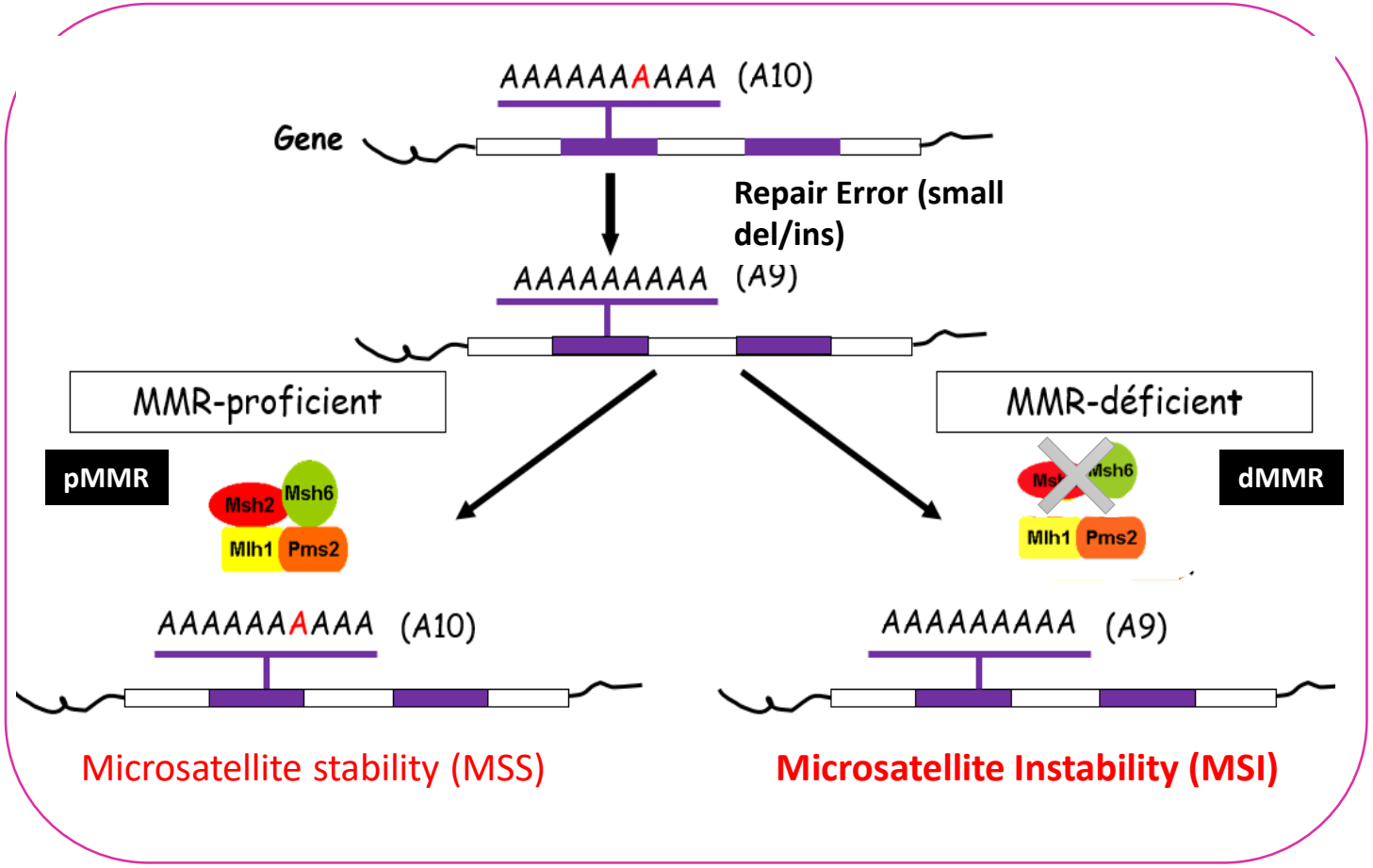
Oncopole

MMR system = MisMatch Repair



DNA Mismatch Repair system

Mismatches : **microsatellites**

4 proteins,
Functional **heterodimers** :

- MSH2/MSH6
- PMS2/MLH1

dMMR : role in oncogenesis

Indications for somatic MMR testing:

Lynch syndrome
screening

Prognosis factor for Colorectal and (gastric, endometrial) cancer:
(neo) adjuvant chemotherapy ?

All M+ cancers :
anti PD1/PDL1 Immunotherapy
Clinical trials ++

Increasing of the indications ++
Not only colorectal / endometrial cancers

Methods used in clinical practice

Molecular Biology (MB)	Immunohistochemistry (IHC)
• **MSI high** : instability **≥ 2** microsatellites • **MSI low** : **1** unstable microsatellite • **MSS** : **5** stable microsatellites *[* Pentaplex PCR , NCI panel *(1)]*	**Testing 4 MMR proteins** MLH1/PMS2, MSH2/MSH6: **Retained staining: pMMR** **Loss of protein staining : dMMR**

Sensitivity / Concordance :

- IHC : **sensitive** (92.3%), very **specific** (100%) *(2)*
- **Concordance IHC/ MB** : 95 to 99 % *(3, 4)*

(1) Xicola RM et al. J Natl Cancer Inst. 2007
(2) Lindor NM et Al. J Clin Oncol. 2002
(3) Cicek MS et Al.. J Mol Diagn. 2011
(4) Bonnet et al. Dig Liver Dis. 2012

The dMMR profiles

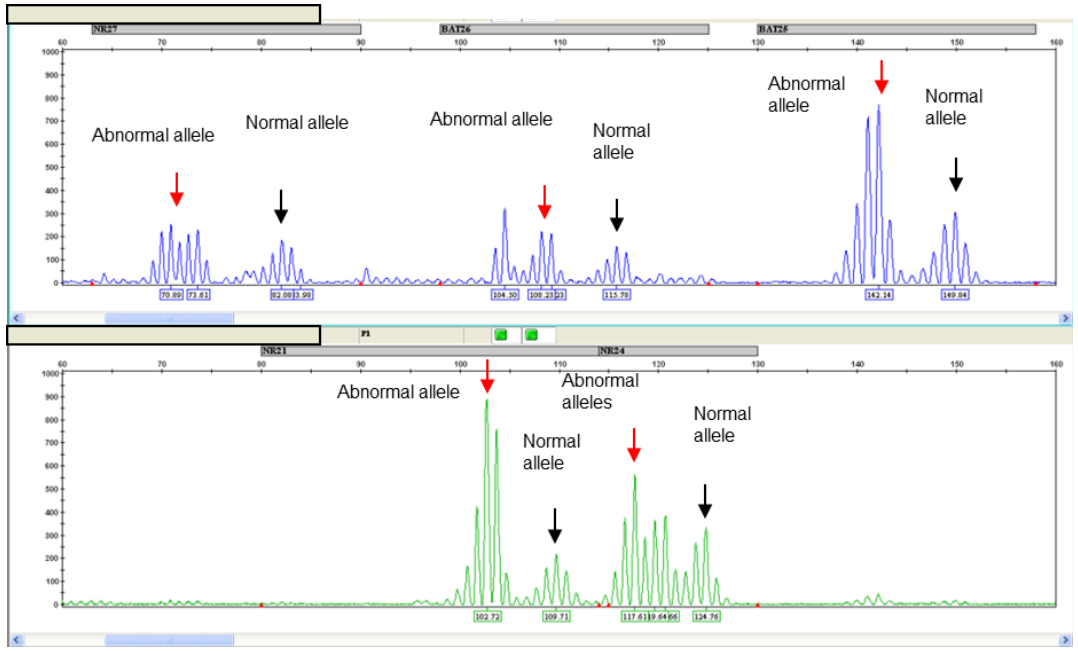
Classical pattern

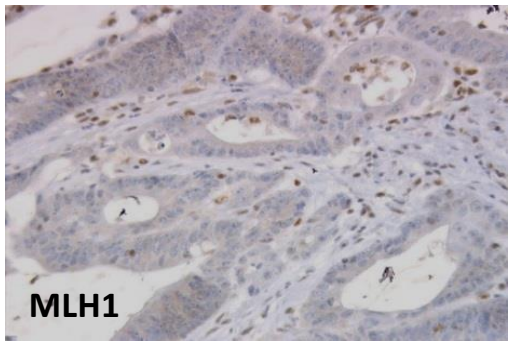
MB

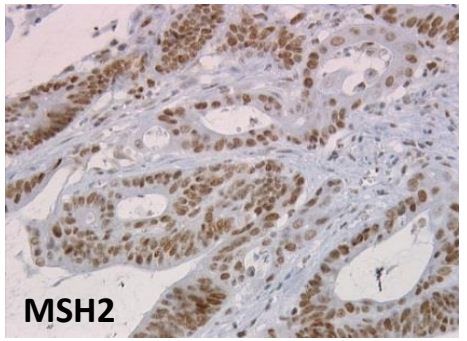
MSI-H

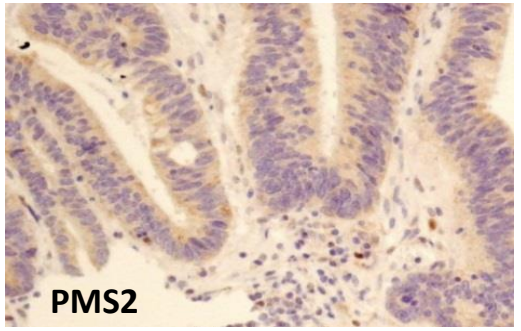
IHC

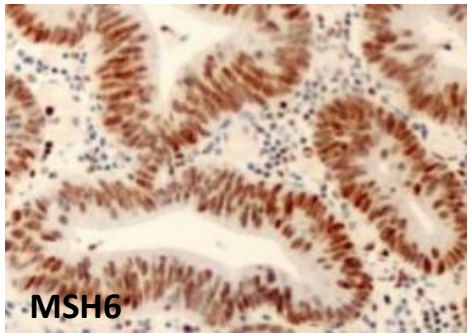
Coupled loss of proteins:
MLH1/PMS2
MSH2/MSH6











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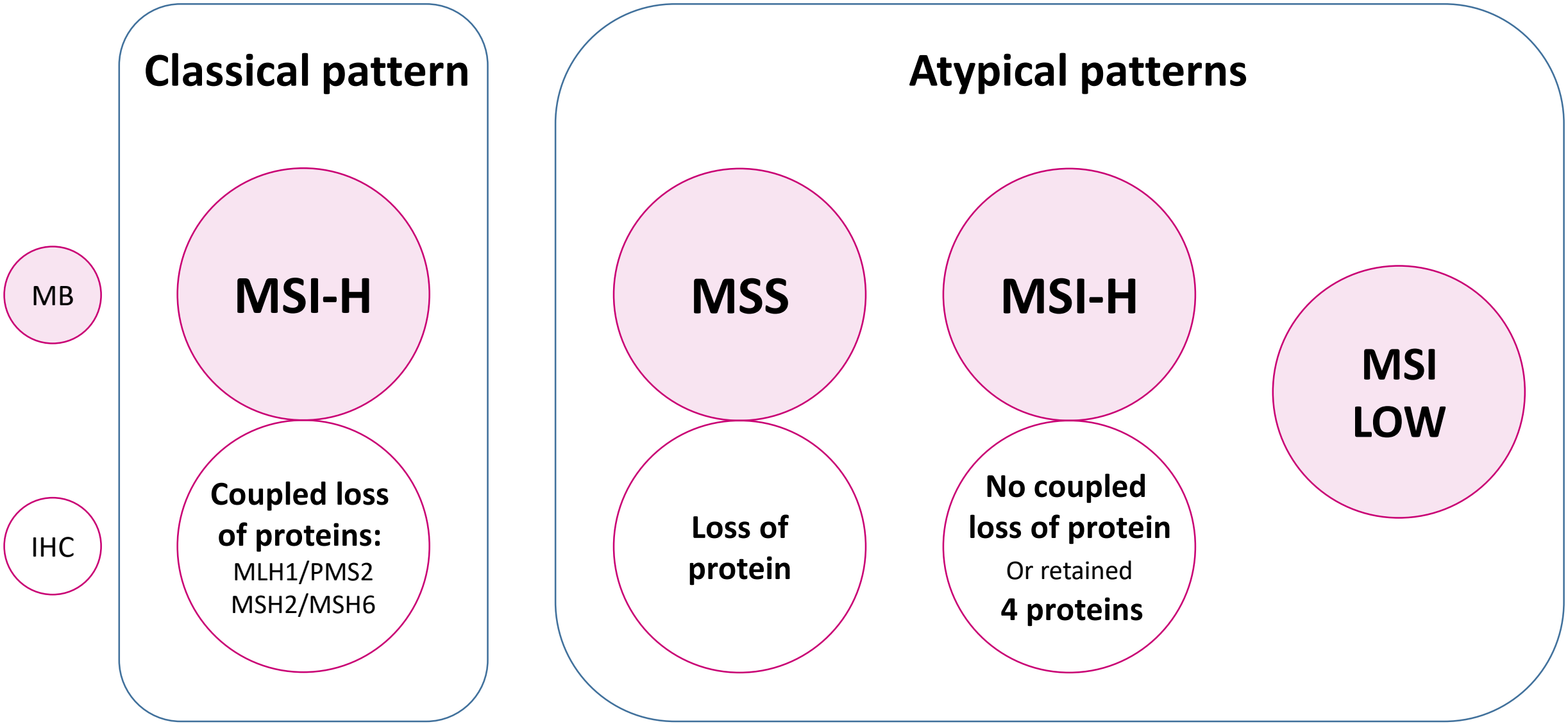
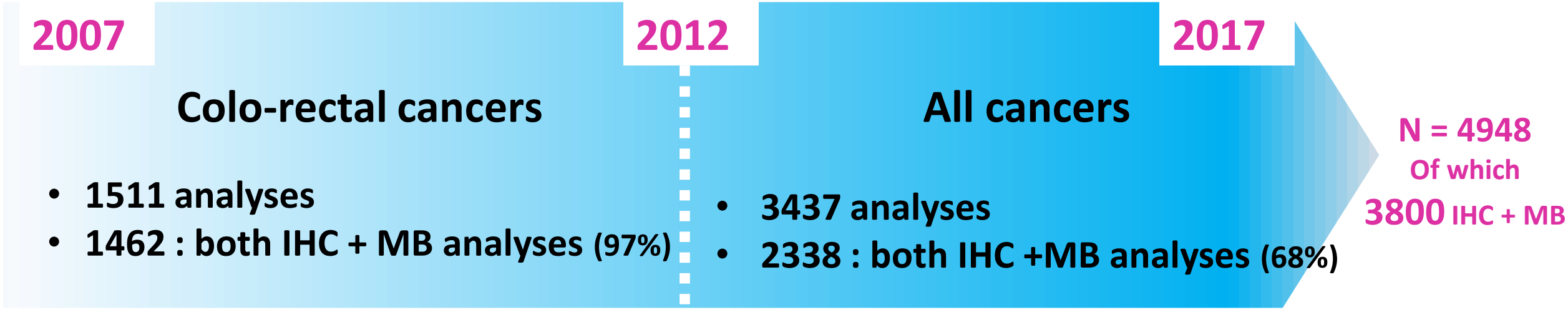


Materials & Methods

- All MMR testing performed between **2007 and 2017**
- **Cancer Molecular Biology Platform** of Midi-Pyrénées



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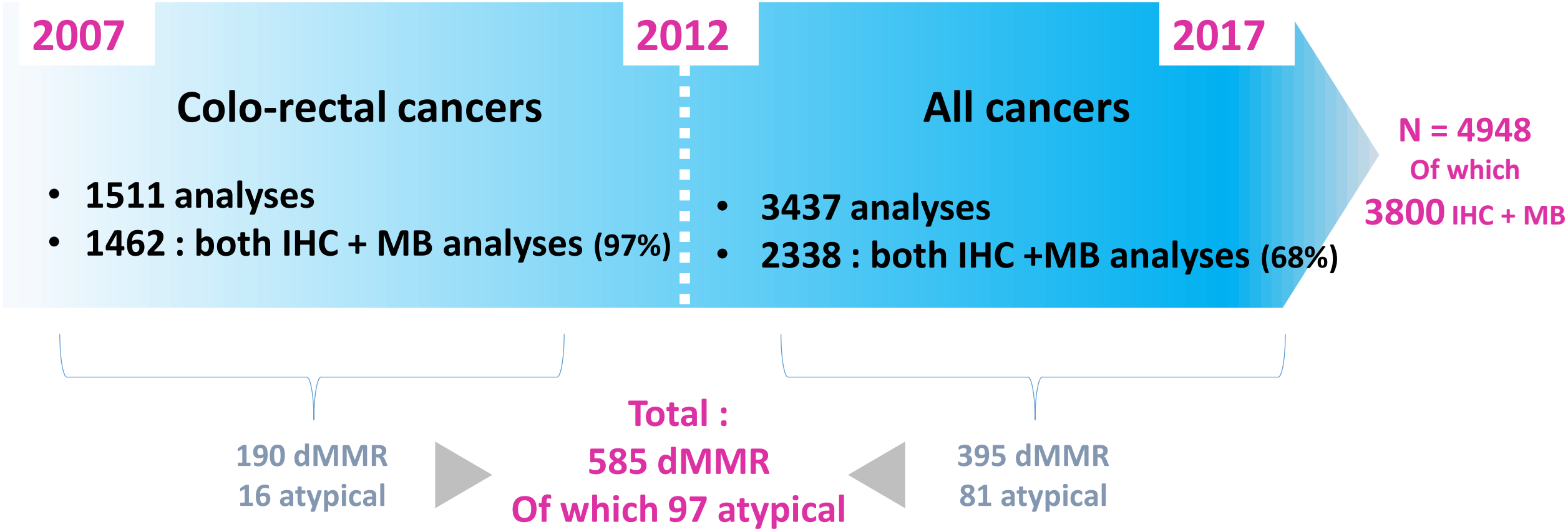
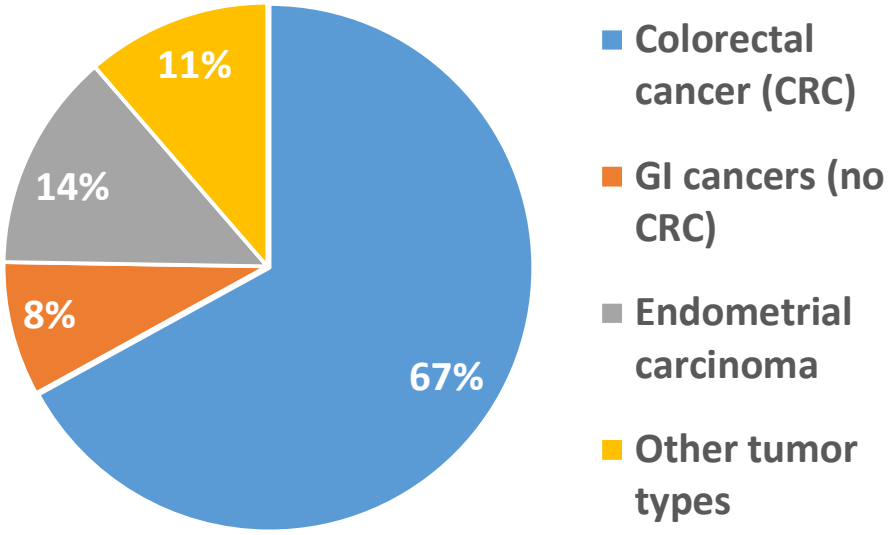
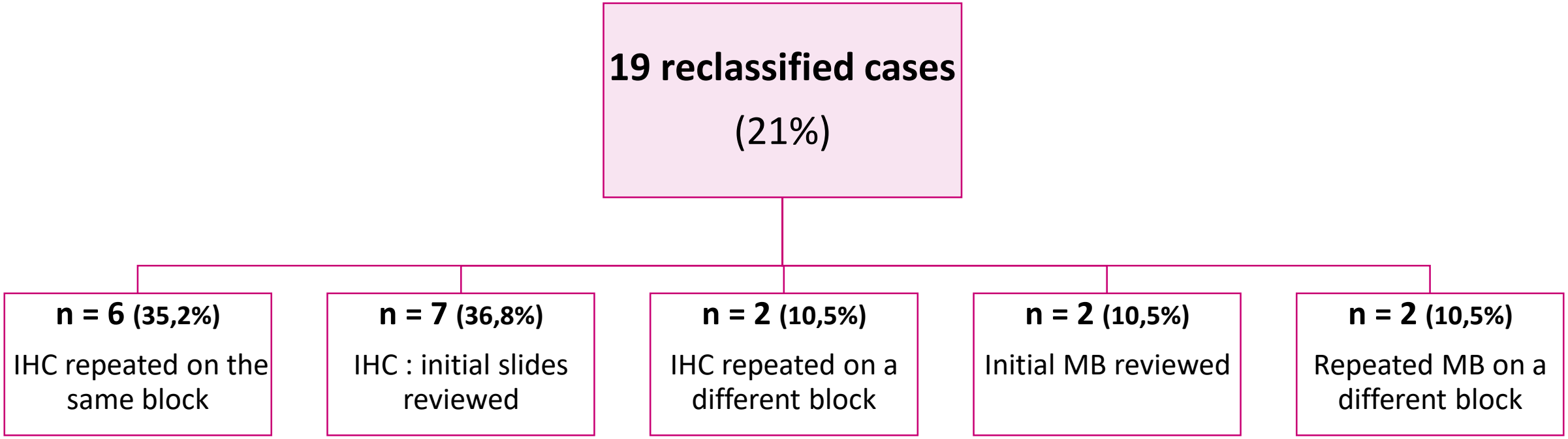


Results (n = 97 atypical dMMR)



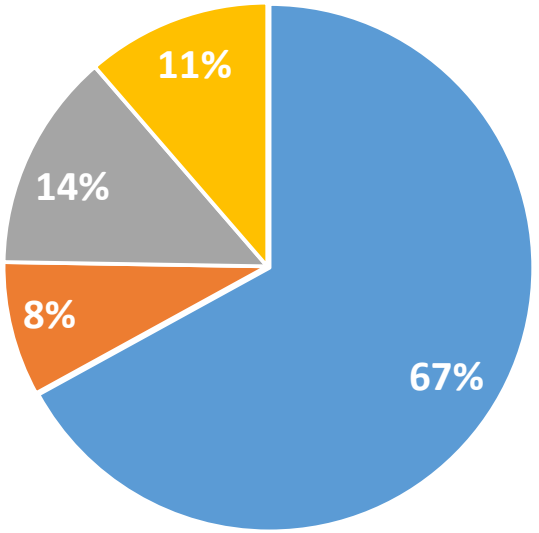
Controls of the analyses (n = 90/97)



After reviewing : **8 cases were reclassified as typical** (5 colons, 3 endometrium)

89 atypical dMMR cases were confirmed = 15%

Results (n = 89 atypical dMMR)



- Colorectal cancer (CRC)
- GI cancers (no CRC)
- Endometrial carcinoma
- Other tumor types

PMS2 or MSH6 **Isolated loss** n = 53	**Classical coupled loss of two proteins** n = 16	**Retained expression of 4 proteins** n = 5	**Aberrant Loss of protein expression** n = 15
43 MSI-H		3 MSI-H	13 MSI-H
1 MSI low	8 MSI low	2 MSI low	0 MSI low
9 MSS	8 MSS		2 MSS

43 cases with a known biological mechanism = « atypical already described » (1,2)

46 cases: « true atypical »

(1) Alpert L et Al. Arch Pathol Lab Med. Avr 2018
(2) Daria Carmela Loconte et Al. Human Pathology. 2014

Results (n = 89)

PMS2 / MSH6 isolated loss **n = 53**

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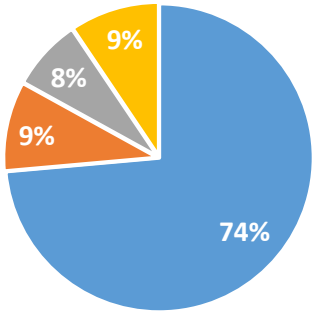
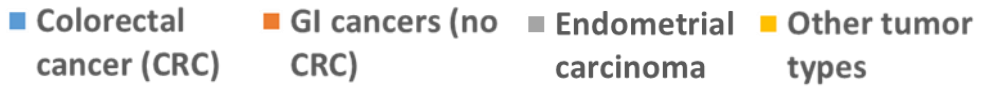
→ 38 **CCR / endometrium**

73 % genetic syndromes

Lynch ++, 1 Pol-E, 1 CMMR-D





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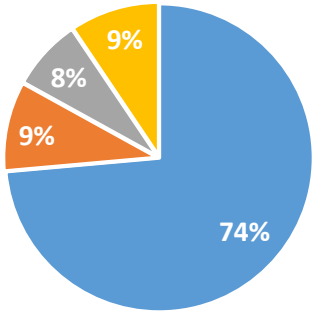

73 % genetic syndromes

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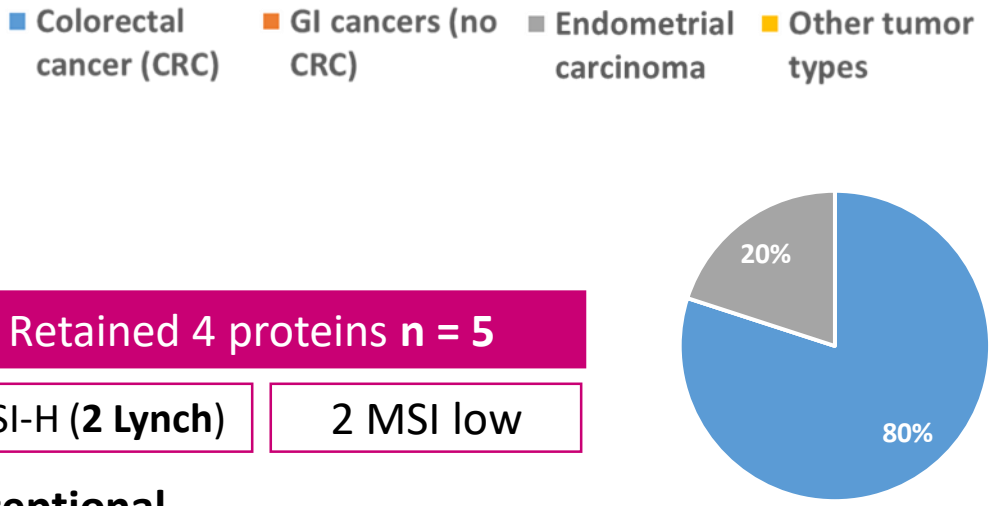
Retained 4 proteins **n = 5**

3 MSI-H (**2 Lynch**)

2 MSI low

Exceptional

Missense mutation ++



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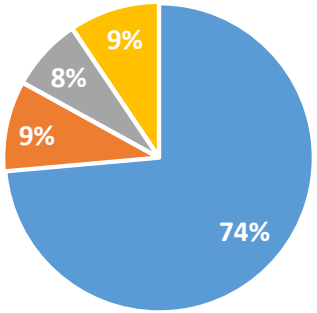

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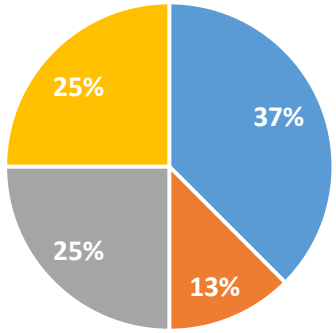

RARE

False negative Pentaplex PCR ?

Mainly no colorectal cancer : 63% of cases

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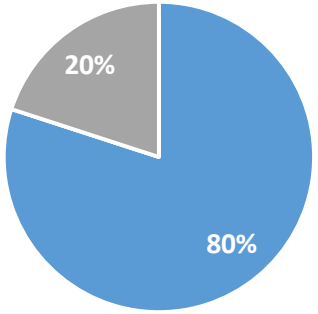

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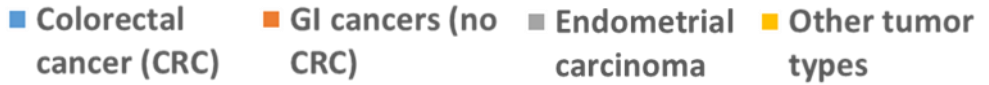

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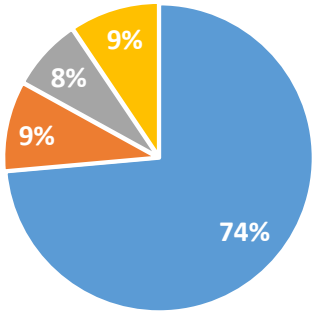

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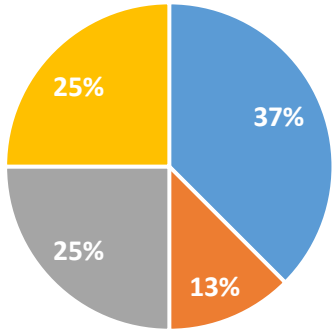

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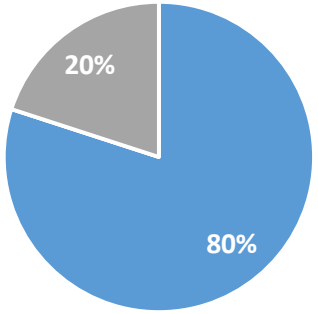
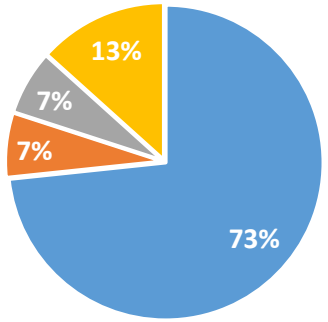


Exceptional

Missense mutations ++

Aberrant loss of protein n = 15

13 MSI-H | 2 MSS



→ MSI ++ : complex mechanism of MMR inactivation ?

4 proteins loss : MLH1 methylation MLH1 + secondary inactivation of MSH6 or MSH2 (1)

(1) Westwood et Al. J Clin Pathol. 2019

Take home messages

- **All atypical results (MB and/or IHC) must be controlled :** to repeat or complete the analyses
- **8% of cases (MB + IHC) are atypical dMMR tumors**

  Increasing for non colorectal cancers

  Strong diagnosis value for Lynch syndrome or genetic syndromes
- **Biological and therapeutic value ?**

  Need to better characterize atypical dMMR cases :
  - Extensive sequencing on going
  - Therapeutic impact for immunotherapy ?

Thank you for your attention !