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Hereditary CRC syndromes

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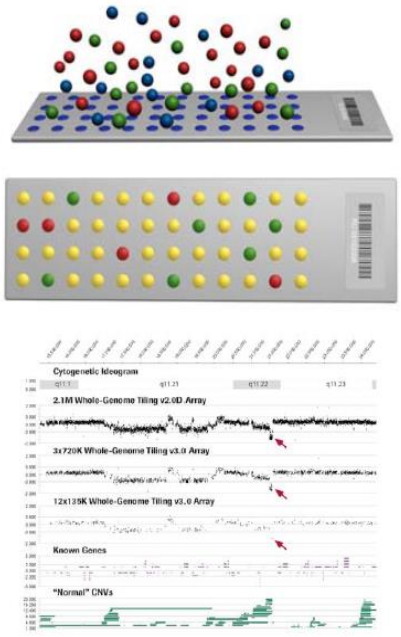
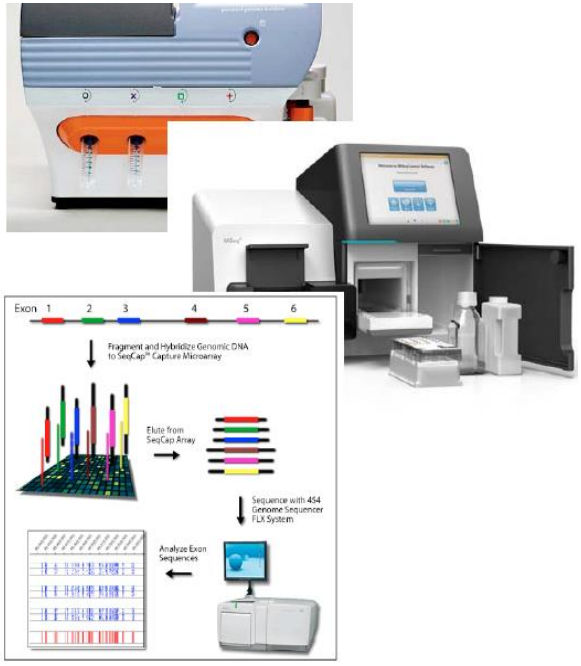
Slightly more than 100 years ago...

Dr. Aldred Scott Warthin

Family G

Warthin, Arch Intern Med 1913

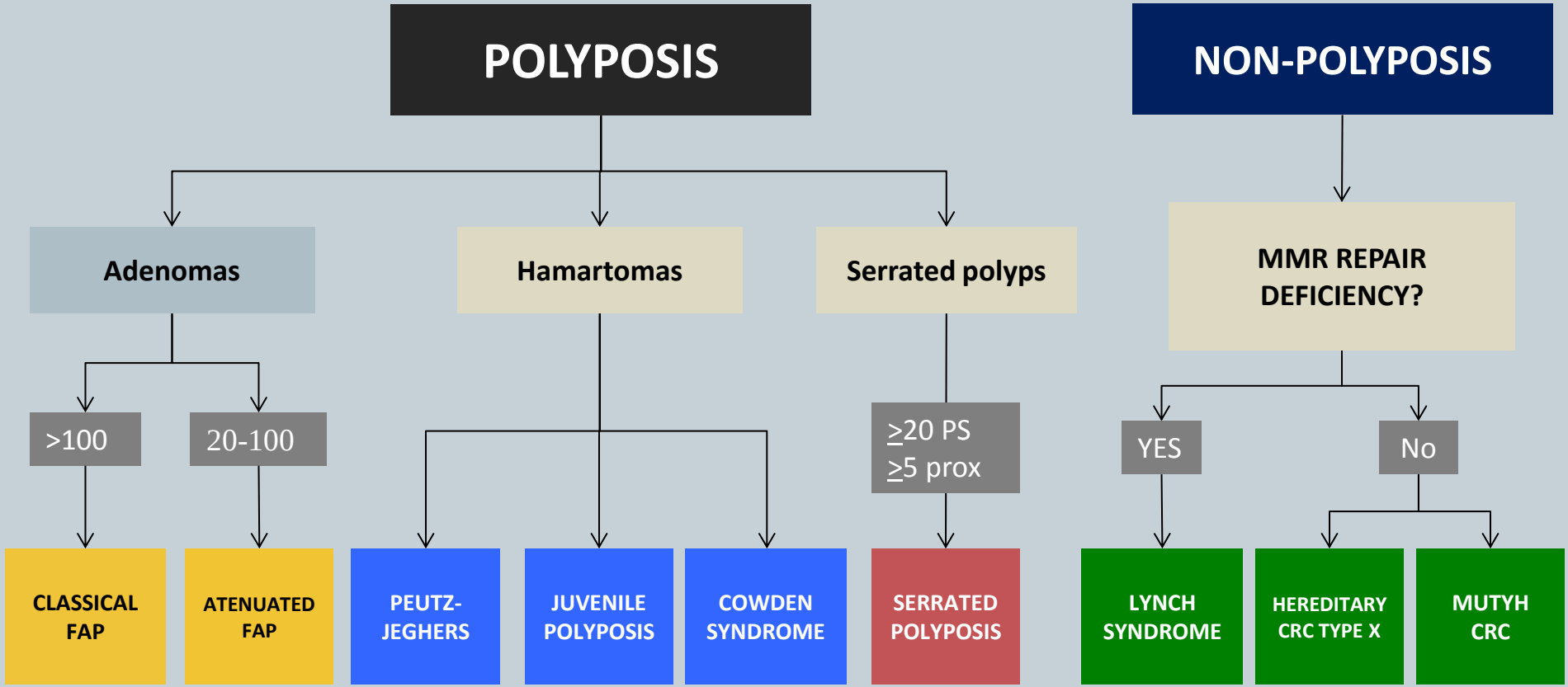

Cytogenetic Ideogram
2.1M Whole-Genome Tiling v2.0D Array
3x720K Whole-Genome Tiling v3.0 Array
12x135K Whole-Genome Tiling v3.0 Array
Known Genes
"Normal" CNVs


Exon 1 2 3 4 5 6
Fragment and Hybridize Genomic DNA to SeqCap® Capture Microarray
Elute from SeqCap Array
Sequence with 454 Genome Sequencer FLX System
Analyze Exon Sequences

Why Would We Consider Germline Genetic Testing in Patients With Cancer?

- Estimation of the **cumulative risk** of cancer in an individual and/or her family
- Identification of individuals at sufficient risk to consider **enhanced screening or prevention strategies**
- Identification of tumors that might respond to **specific therapies**

Hereditary CRC: genetic heterogeneity



Courtesy Dr Balaguer

A 2016 clinical case...

A 43 year old patient with stage II right-sided CRC. The pathology report described that her tumor had MSI and loss of MLH1 protein expression. A tumor genetic profiling analysis revealed a hypermutated phenotype (1000 somatic mutations). The patient reports a family history of endometrial cancer in her mother. She is seeking advice to find out if her children must undergo surveillance with colonoscopy

- ✓ Is this suspicious of a hereditary cancer syndrome?
- ✓ If so, what other molecular/genetic tests would you recommend to her?
- ✓ What type of surveillance would you recommend in her and her close family members?

MSI and loss of expression of MLH1

- ✓ MSI is present in 10-15% of sporadic CRC, mainly due to somatic tumor *MLH1* promoter methylation
- ✓ *MLH1* promoter methylation is correlated with tumor *BRAF V600E* mutation

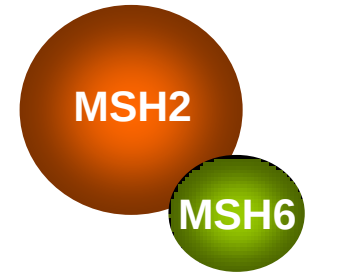
CRC cases	BRAF mutation	MLH1 "C" region methylation
550 MMR germline mutation +	1.4% (0.06-3%)	6%
1623 MMR mutation – with MSS	5% (4-7%)	NA
332 MMR germline mutation – with MSI/ MLH1 expression loss	63.5% (47-79%)	47% (P<0.0001)

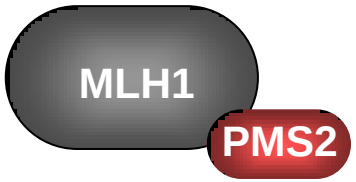
Parsons, J Med Genet 2012

Immunostaining interpretation

Combinatorial IHC testing of all four MMR proteins can provide an **indication of the specific MMR gene that is most likely to contain a pathogenic germline mutation**:

- Dual loss of MLH1 and PMS2 protein expression suggest a germline mutation within *MLH1* as the PMS2 protein is not stable in the absence of MLH1.
- IHC loss of both MSH2 and MSH6 staining implies a germline mutation within *MSH2*.

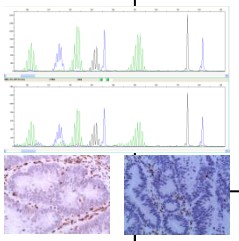




Germline mutated gene	Immunostaining			
	MSH2	MSH6	MLH1	PMS2
MSH2	-	-	+	+
MSH6	+	-	+	+
MLH1	+	+	-	-
PMS2	+	+	+	-

Piñol et al. JAMA 2005

Non-polyposis CRC: Universal MMR deficiency testing



CRC patient

Tumor mismatch repair deficiency?

Loss of MLH1

Somatic *BRAF*?

mutated

Sporadic MSI CRC
Non hereditary

wt

Loss of MSH2/MSH6/PMS2

Germline testing

+

Lynch syndrome

-

Lynch-like syndrome

Retained expression/MSS

Lynch syndrome very unlikely

Hampel et al. NEJM 2005
Moreira L, Balaguer F *et al.* JAMA 2012
Moreira et al. Cancer 2015

Lynch-like syndrome: what is the cause?

1. **"Cryptic" germline mutations** in the 4 DNA MMR genes in actual Lynch syndrome patients (ie, mutations were present, but not detected)

   EPCAM gene (which is immediately upstream of *MSH2*) (Ligtenberg et al. Nat Genet 2009)

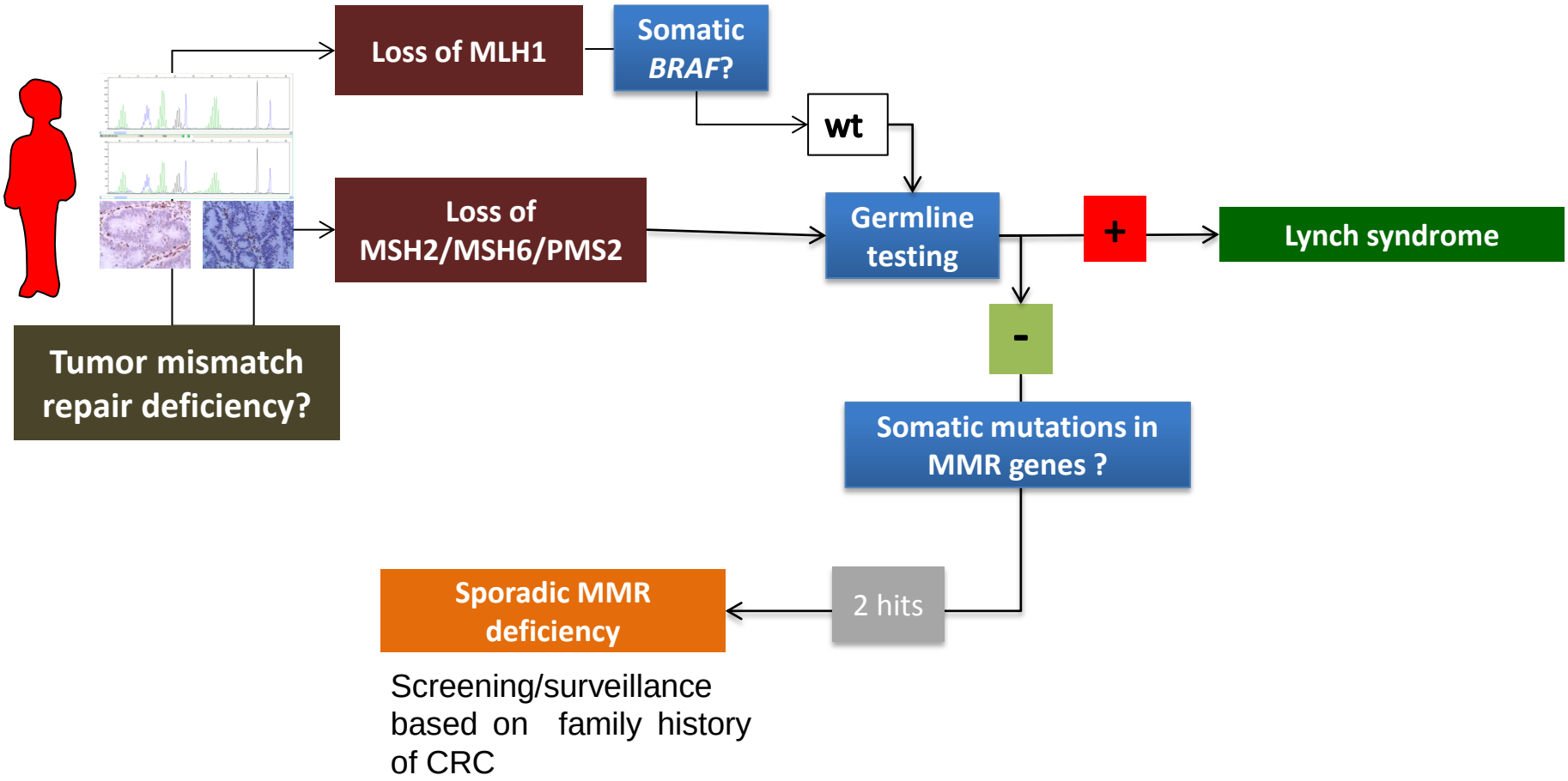
   Other undiscovered genes??

2. **Some pathologic process other than a germline mutation or methylation of a DNA MMR gene that can produce a CRC with MSI.**

   Biallelic somatic mutations of MMR genes (Sourrouille, F et al. Fam Cancer 2013)

Study	N	Tumor types	Cohort	Genes analyzed	Methods	Frequency of 2 somatic mutations
Mesenkamp et al. Gastroenterology 2013	25	23 CRC 2 EC	Clinic-based	*MLH1* *MSH2*	Sanger LOH	**13/25 (52%)**
Haraldsdottir S et al. Gastroenterology 2014	32	18 CRC 14 EC	Population-based	*MLH1* *MSH2* *MSH6* *PMS2*	Coloseq (NGS) LOH	**22/32 (69%)**
Geurts-Giele et al. Jounal of Pathology 2014	40	35 CRC 4 EC 1 ovary	Clinic-based Population-based	*MLH1* *MSH2* *MSH6* *PMS2*	NGS LOH	**26/40 (65%)**

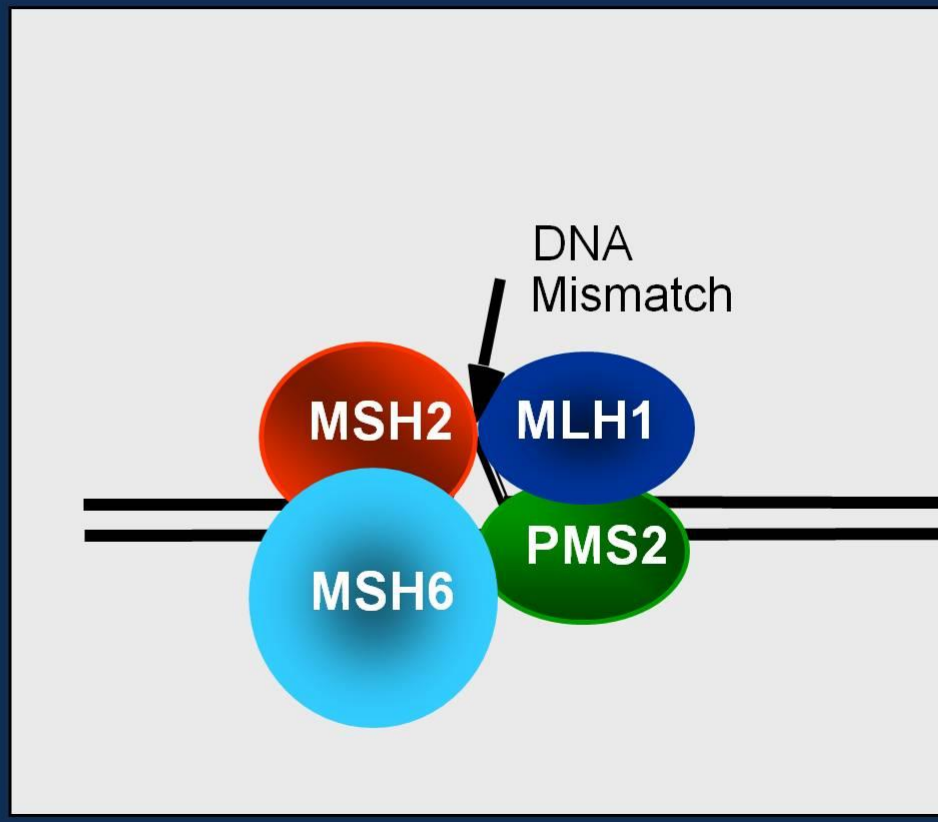
Non-polyposis CRC:
Updated universal MMR deficiency testing



Screening/surveillance based on family history of CRC

Etiologies of Mismatch Repair Deficiency (MMR-d)

- Somatic
  - *BRAF* mutation
  - *MLH1* promoter hypermethylation
  - **Mutations in DNA MMR genes**
    - **"Lynch-like or Tumor Lynch"**
- Germline mutations in DNA MMR Genes
  - Lynch Syndrome

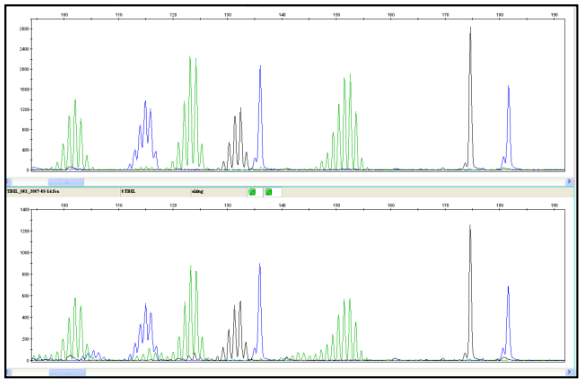


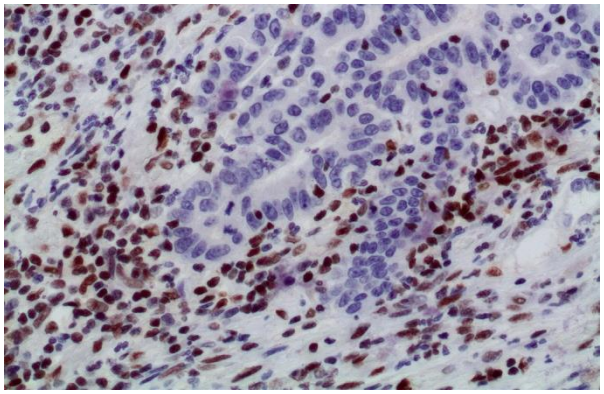
Lynch syndrome (formerly known as HNPCC)

- **Most common hereditary CRC syndrome** (3-5%)
- **Cause**:
- Germline mutations in MMR genes (*MLH1/MSH2/MSH6/PMS2/Epcam*)
- Autosomal dominant pattern of inheritance (50% probability of transmission)

- **Clinical phenotype:** cancer predisposition (early-onset, but not always…..)
  - Lifetime risk of CRC: 25-80%
  - Lifetime risk of endometrial cancer: 20-70%
  - Others: stomach, urinary tract, ovary, small bowel

- **Tumor phenotype**:
  - Characteristic pathology: tumor infiltrating lymphocytes, mucinous features
  - **Microsatellite instability** (MSI) (PCR-based assay)
  - **Loss of protein expression** (immunohistochemistry)



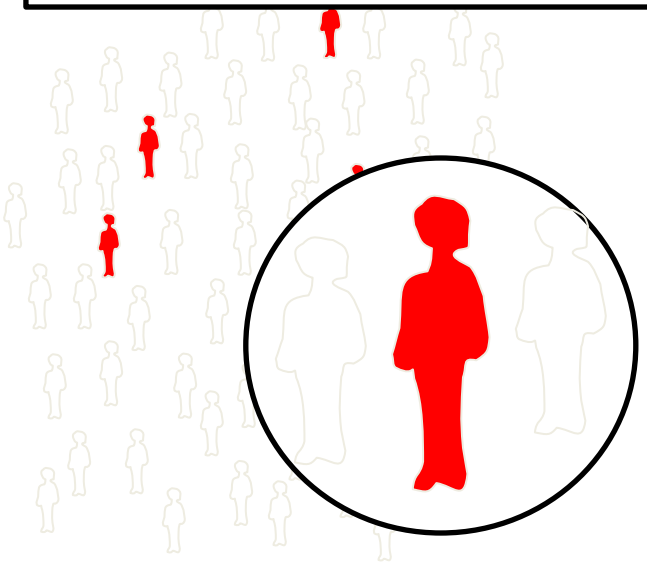


Hampel et al. NEJM 2005
Piñol et al. JAMA 2005
Bessa X et a. JCO 2011

Lynch syndrome: Underdiagnosis

Main cause of underdiagnosis: **absence of clinical suspicion**

- <50% of cancer centers perform IHC testing or MSI routinely *(Beamer et al. JCO 2012)*
- Family history remains largely unrecognized *(Grover et al. CGH 2004; Singh et al. CGH2010)*
- Lynch syndrome often does not show a significant family history



- Prevalence in general population: 1/1000-1/2000
- Prevalence in CRC patients: 1-5/100
- World incidence: 30.000 new cases/year

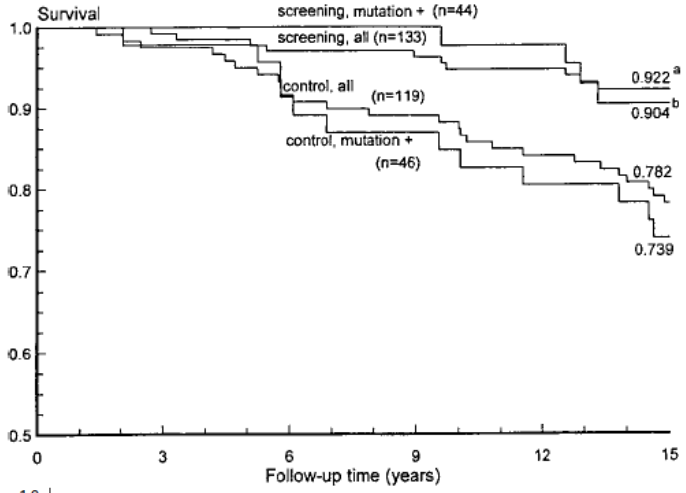
Impact of LS diagnosis

PREVENTIVE SETTING:

COLONOSCOPY 3 y vs No

Järvinen et al, Gastroenterology 2000

RR: 0.35 (0.12-0.99)

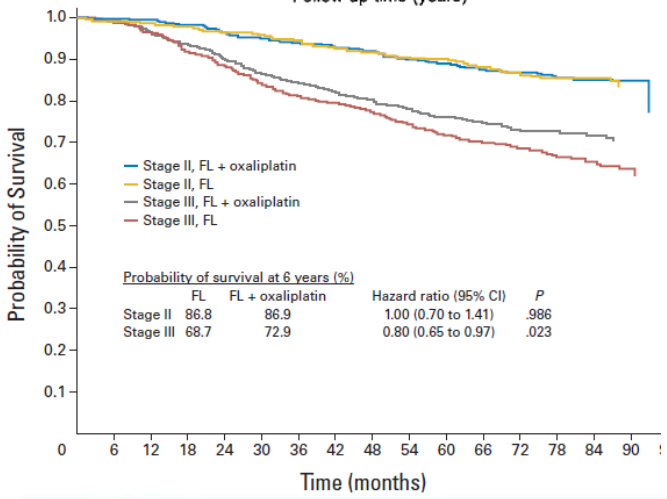


ADJUVANT SETTING:

FOLFOX 4 vs 5FU-LV

MOSAIC; André et al, JCO 2009

HR: 0.80 (0.66-0.97)



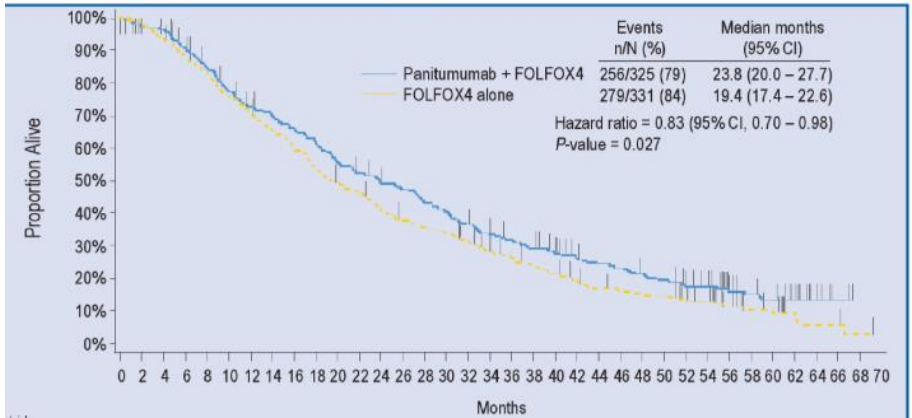
METASTATIC SETTING:

FOLFOX 4 vs FOLFOX4+PANITUMUMAB

(wild type *KRAS*)

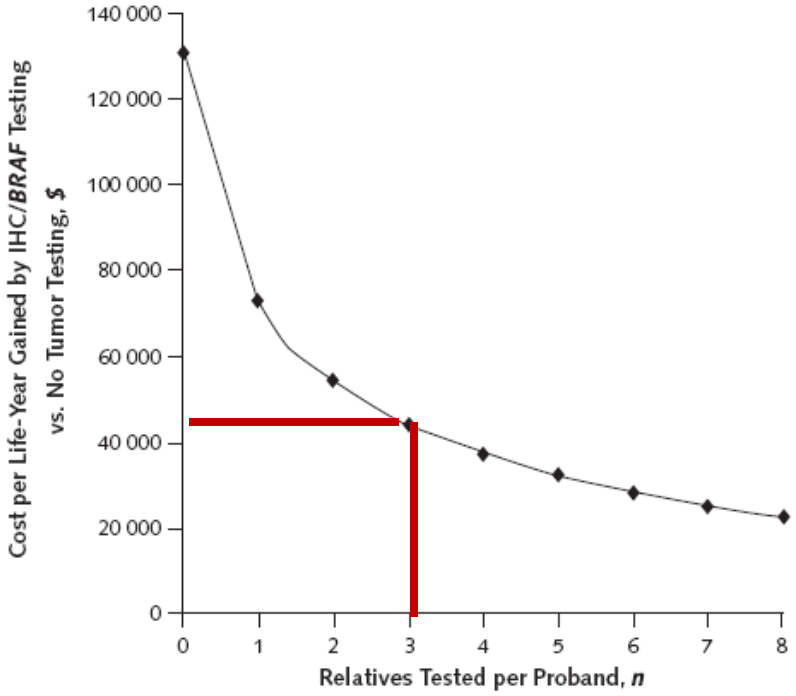
PRIME; Douillard et al, ASCO 2013

HR: 0.83 (0.70- 0.96)



Cost-effectiveness

Strategy	Discounted Life-Years per Person	Discounted Cost per Person, $	Colorectal Cancer Cases (Deaths) per 100 000 Persons, *n* (*n*)	Endometrial Cancer Cases (Deaths) per 100 000 Persons, *n* (*n*)	Ovarian Cancer Cases (Deaths) per 100 000 Persons, *n* (*n*)	Discounted Incremental Cost per Life-Year Gained, $†	Discounted Incremental Cost per Life-Year Gained, Excluding Clinical Criteria Strategies, $†
IHC with *BRAF* testing	23.7319	19 381	21 753 (5080)	9819 (1645)	1827 (961)	–	36 200
Up-front germline testing	23.8047	33 492	19 736 (4320)	9694 (1624)	1803 (948)	293 000	293 000



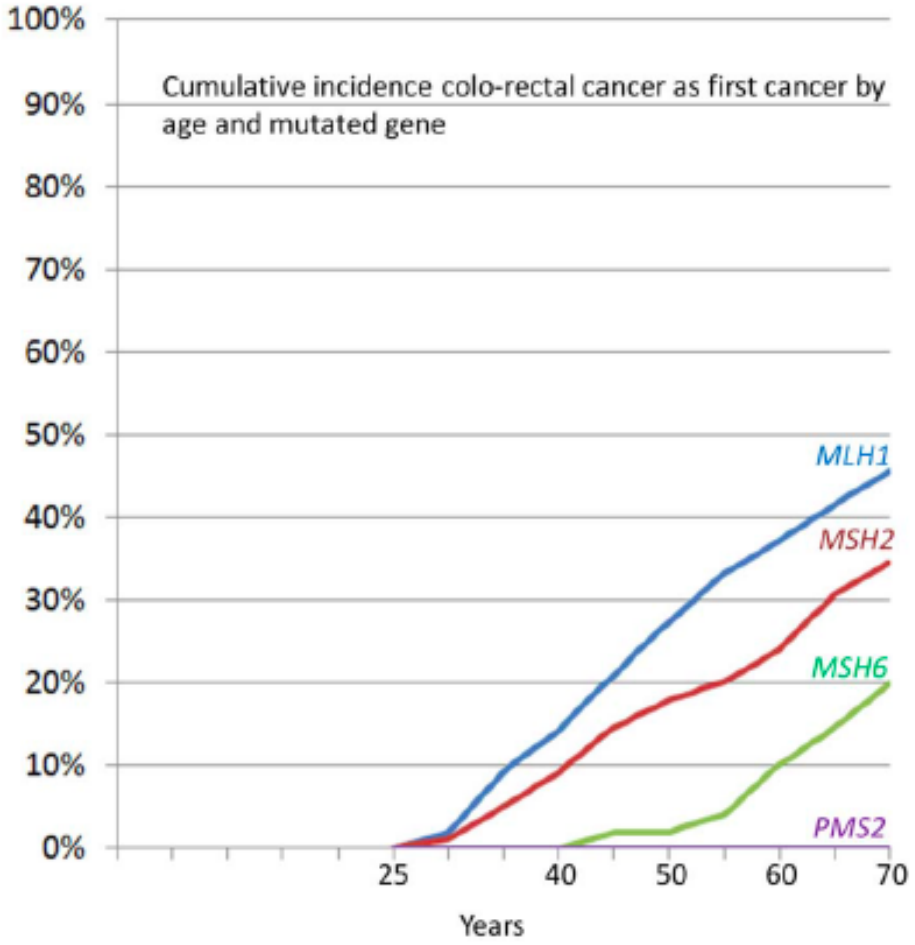
Among tumor-testing strategies, IHC with *BRAF* testing had an incremental cost-effectiveness ratio <$50 000 per life-year gained when 3 relatives but not when 2 relatives were tested per proband. IHC = immunohistochemistry.

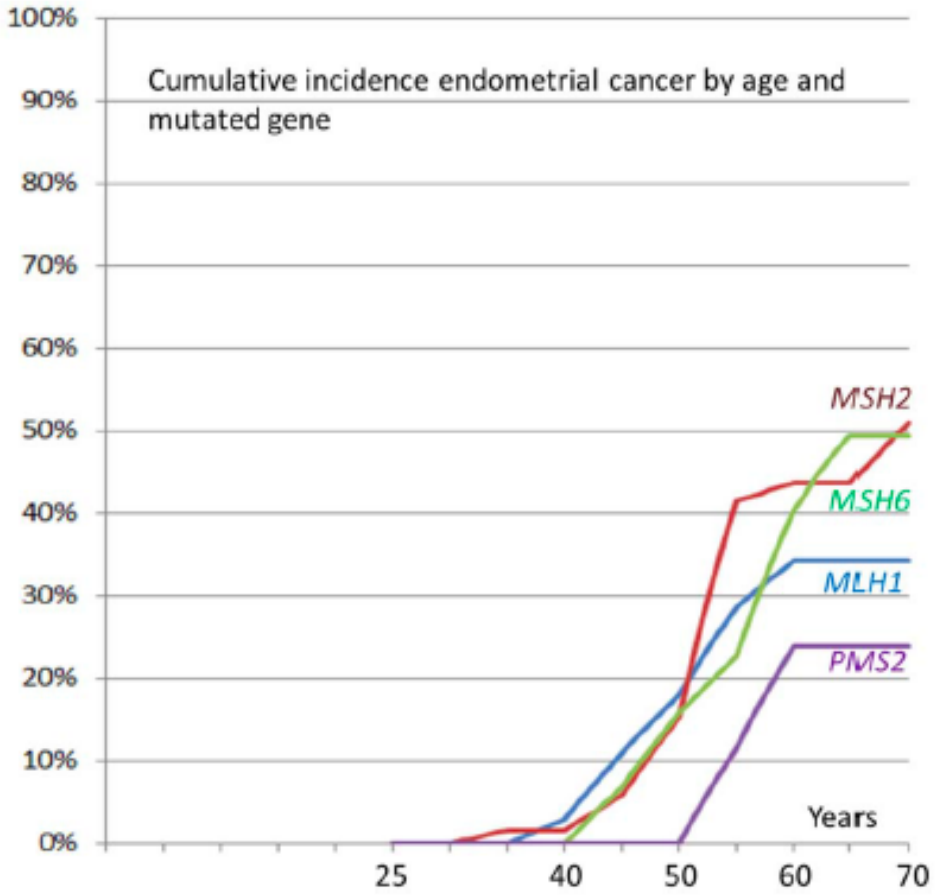
Ladabaum, Arch Int Med 2011

Three critical current clinical questions in LS

- What is the **cumulative risk** by age to first cancer?
- In which organs are **first cancers** most likely to occur?
- What are the **outcomes** for these cancers?

1942 mutation carriers undergoing prospective cancer surveillance





Moller et al, Gut 2015

Time since last colonoscopy	
mean	median
32 months	27 months (7-123)

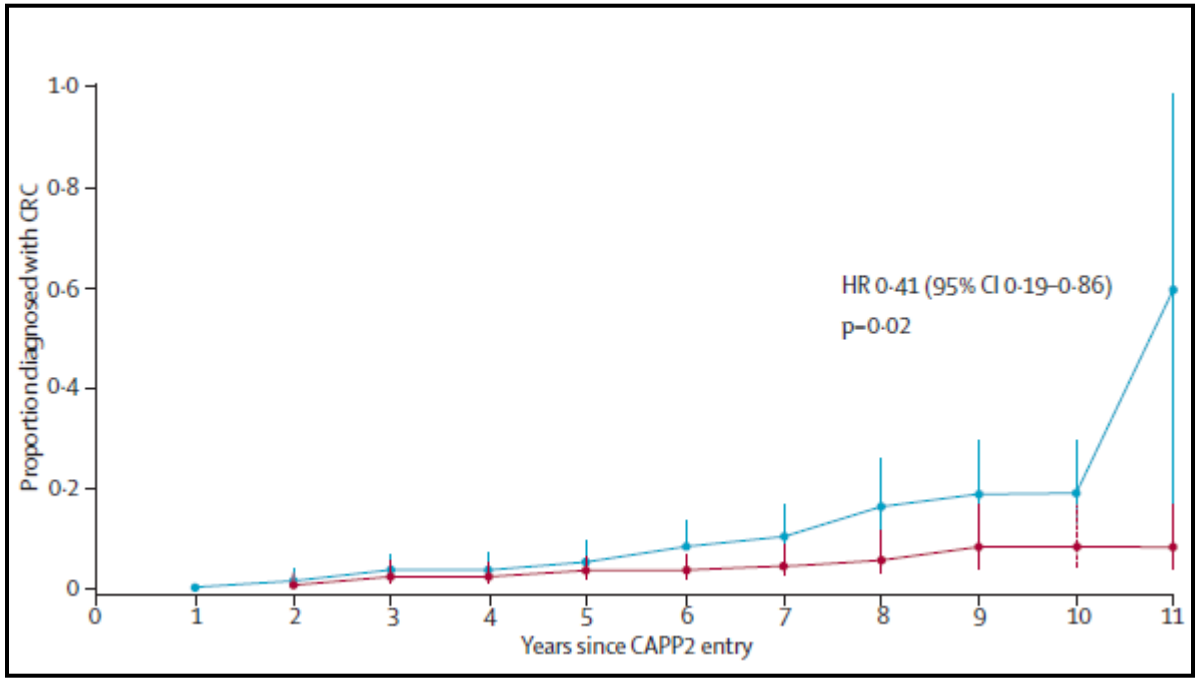
Cumulative % of CRC since last colonoscopy	
Up to 12 months	Up to 24 months
6%	31%

Table 7 5-year and 10-year crude survival after first cancer diagnosed by cancer type in Lynch syndrome (LS) patients without prior or prevalent cancer at first colonoscopy

Group	Number cases	5-year survival (95% CI)	10-year survival (95% CI)
Any cancer	301	90% (86 to 93)	87% (83 to 91)
Colorectal cancer	140	94% (90 to 98)	91% (84 to 95)
Endometrial cancer	71	98% (88 to 99.8)	98% (88 to 99.8)
Ovarian cancer	19	88% (60 to 97)	89% (60 to 97)
Upper GI cancer	24	58% (36 to 75)	53% (31 to 71)
Urinary tract cancer	17	82% (51 to 93)	73% (42 to 89)

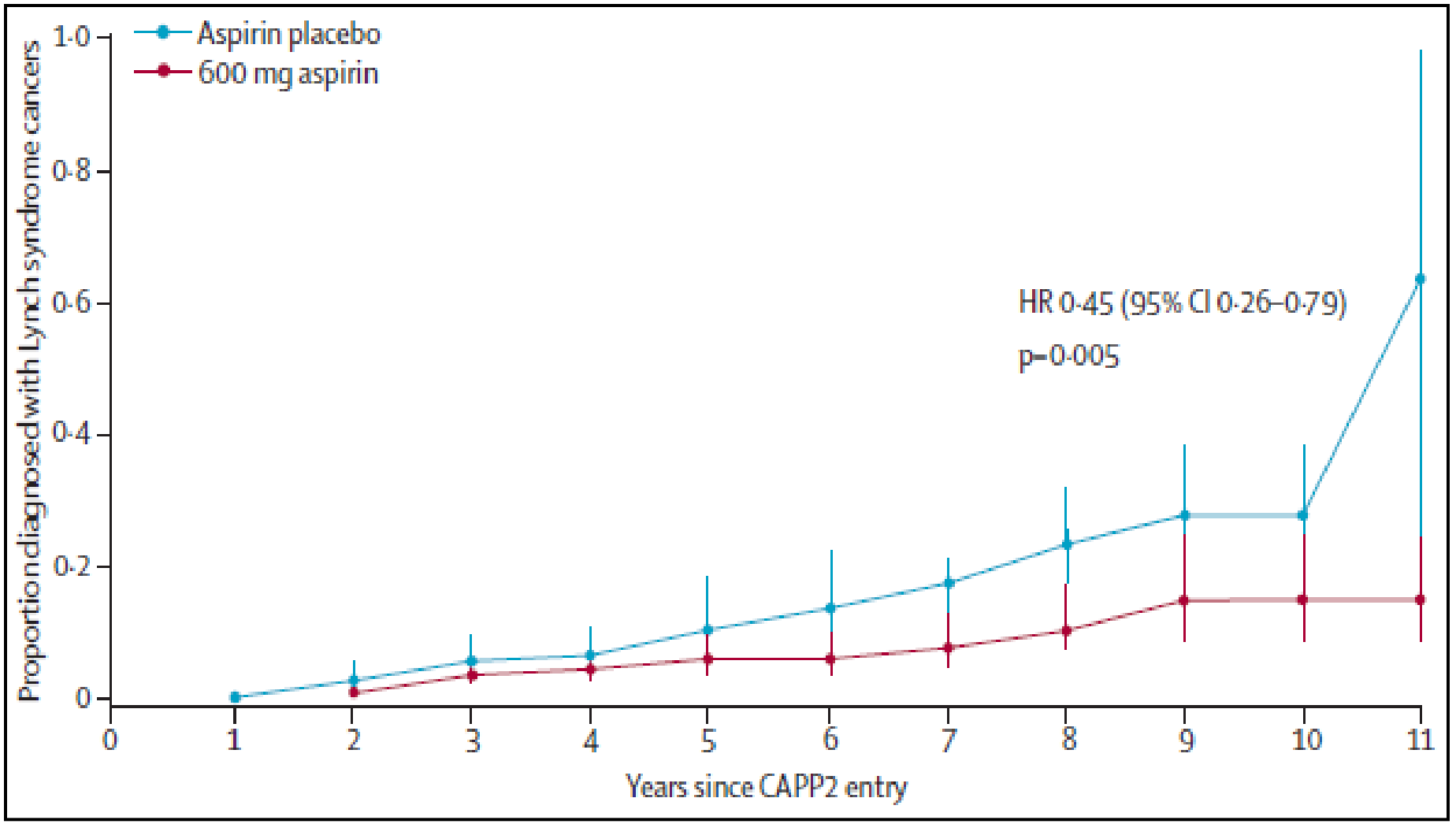
Moller et al, Gut 2015

CAPP2 Study – Aspirin in Lynch S Colon Cancer Risk



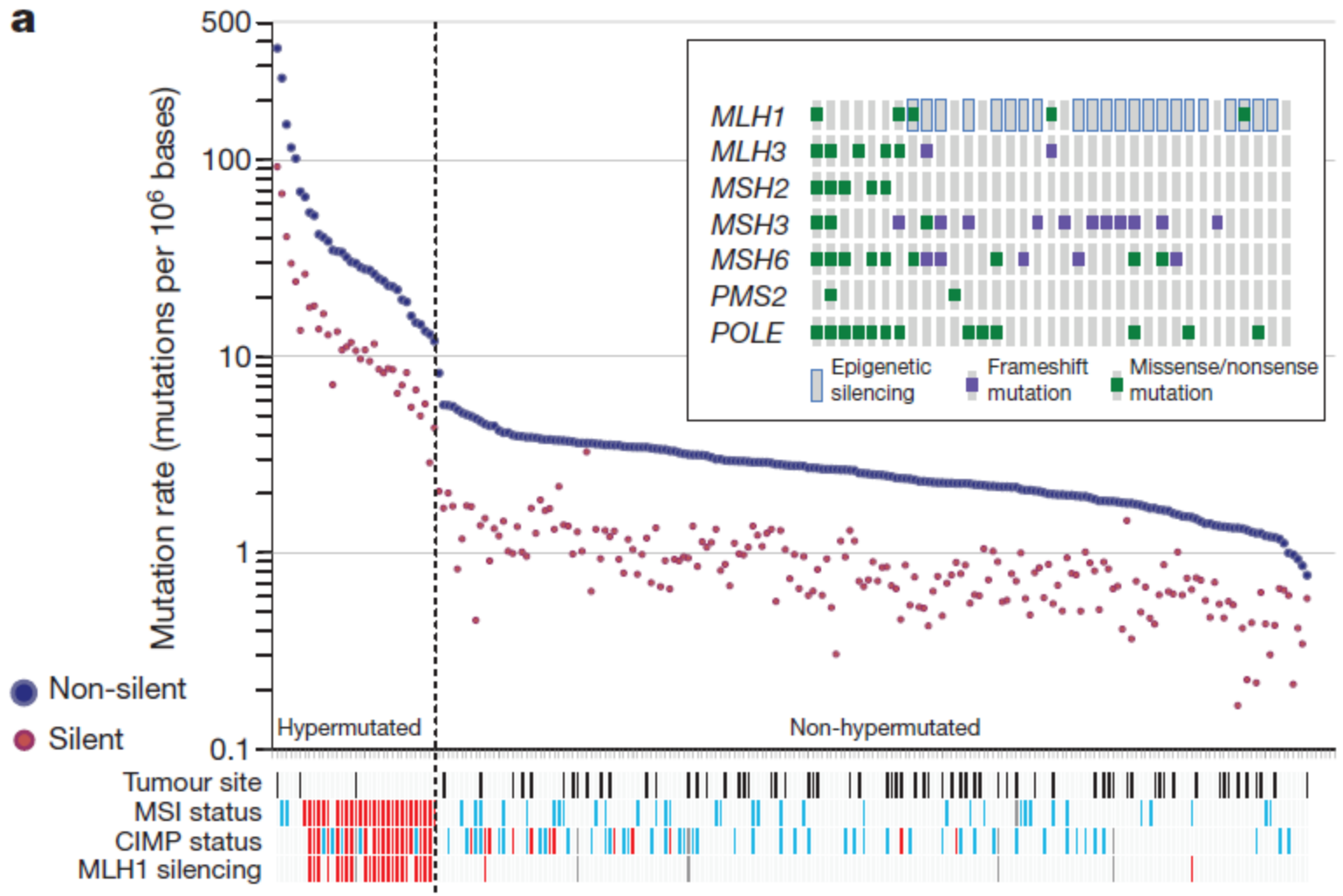
Burns J et al, Lancet (2011)

CAPP2 Study – Aspirin in Lynch S Colon Cancer Risk



Burns J et al, Lancet (2011)

TCGA COLON AND RECTAL CANCER



Nature, 2012

KEYNOTE-016

Study Design

Colorectal Cancers

Cohort A
Deficient in Mismatch Repair (n=28)

Cohort B
Proficient in Mismatch Repair (n=25)

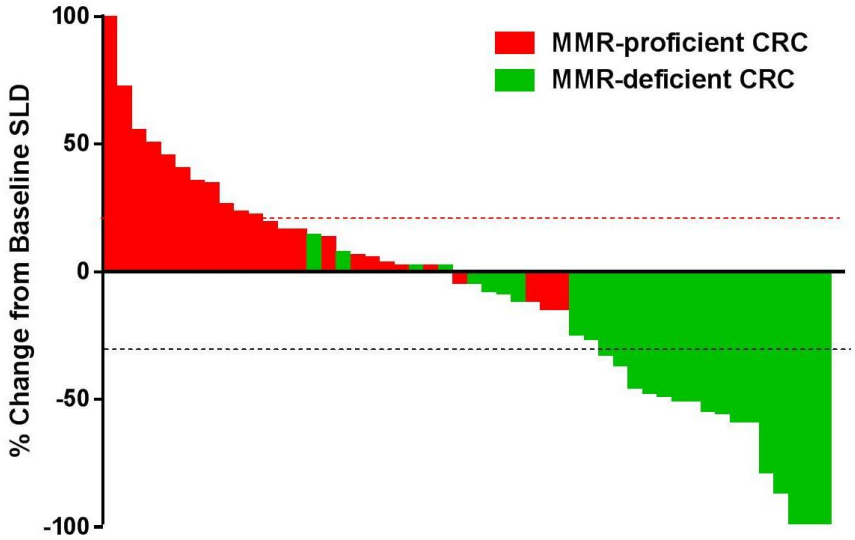
Non-Colorectal Cancers

Cohort C
Deficient in Mismatch Repair (n=30)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Here we report and update from the original 13 CRC Cohort A patients reported at ASCO 2015

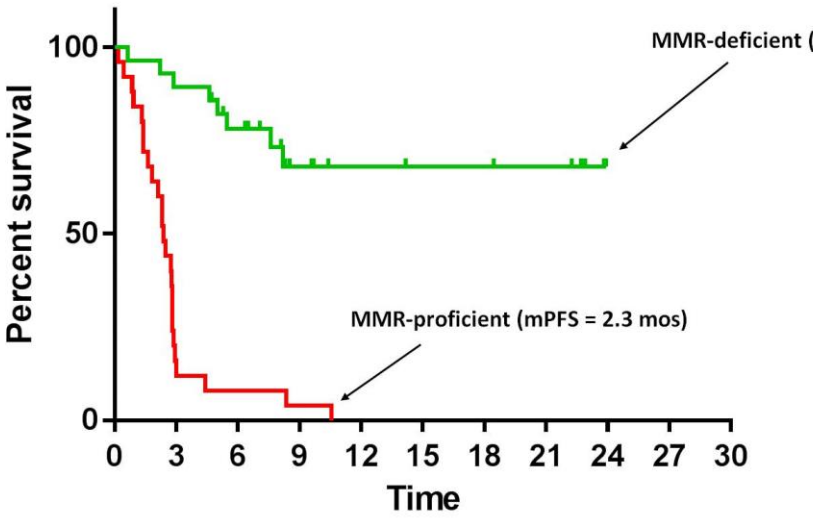
Type of Response-no (%)	MMR-deficient CRC n=28	MMR-proficient CRC n=25
Complete Response	3 (11)	0 (0)
Partial Response	13 (46)	0 (0)
Stable Disease (Week 12)	9 (32)	4 (16)
Progressive Disease	1 (4)	11 (44)
Not Evaluable[1]	2 (7)	10 (40)
Objective Response Rate (%)	16 (57)	0 (0)
95% CI	39 - 73	0 -13
Disease Control Rate (%)	25 (89)	4 (16)
95% CI	73 - 96	6 - 35
Median Follow Up (mos)	9.3	6

Best Radiographic Response

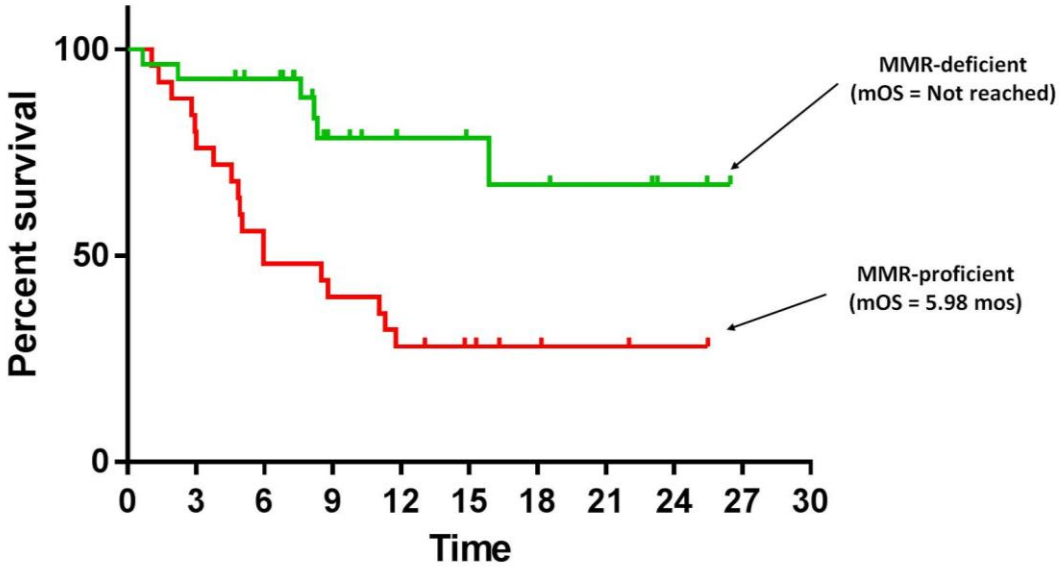


Dung Le at 2016 ASCO

Progression-free Survival



Overall Survival



Presented By Dung Le at 2016 ASCO Annual Meeting

Take home messages

- ✓ **MMR deficiency** might be sporadic (biallelic somatic mutations, MLH1 hypermethylation), or hereditary (LS)
- ✓ MMR deficiency provides predictive information for **therapeutic decision making**
  - ✓ early stage:lack of efficacy of 5-FU
  - ✓ advanced setting: benefit of immune checkpoint blockade
- ✓ Rule out LS after identification of **MMR deficiency:**
  - ✓ **cancer prevention** is possible (second tumors and family members)
  - ✓ **cost-effective**
  - ✓ overall **good** prognosis