

# LYNCH SYNDROME IN ISRAEL

- **Insight from a large, population based, regional cohort**

Gad Rennert, M.D., Ph.D.

Clalit National Cancer Control Center

Dept. of Community Medicine and Epidemiology,

Carmel Medical Center and Technion

Haifa, Israel

# MECC Study

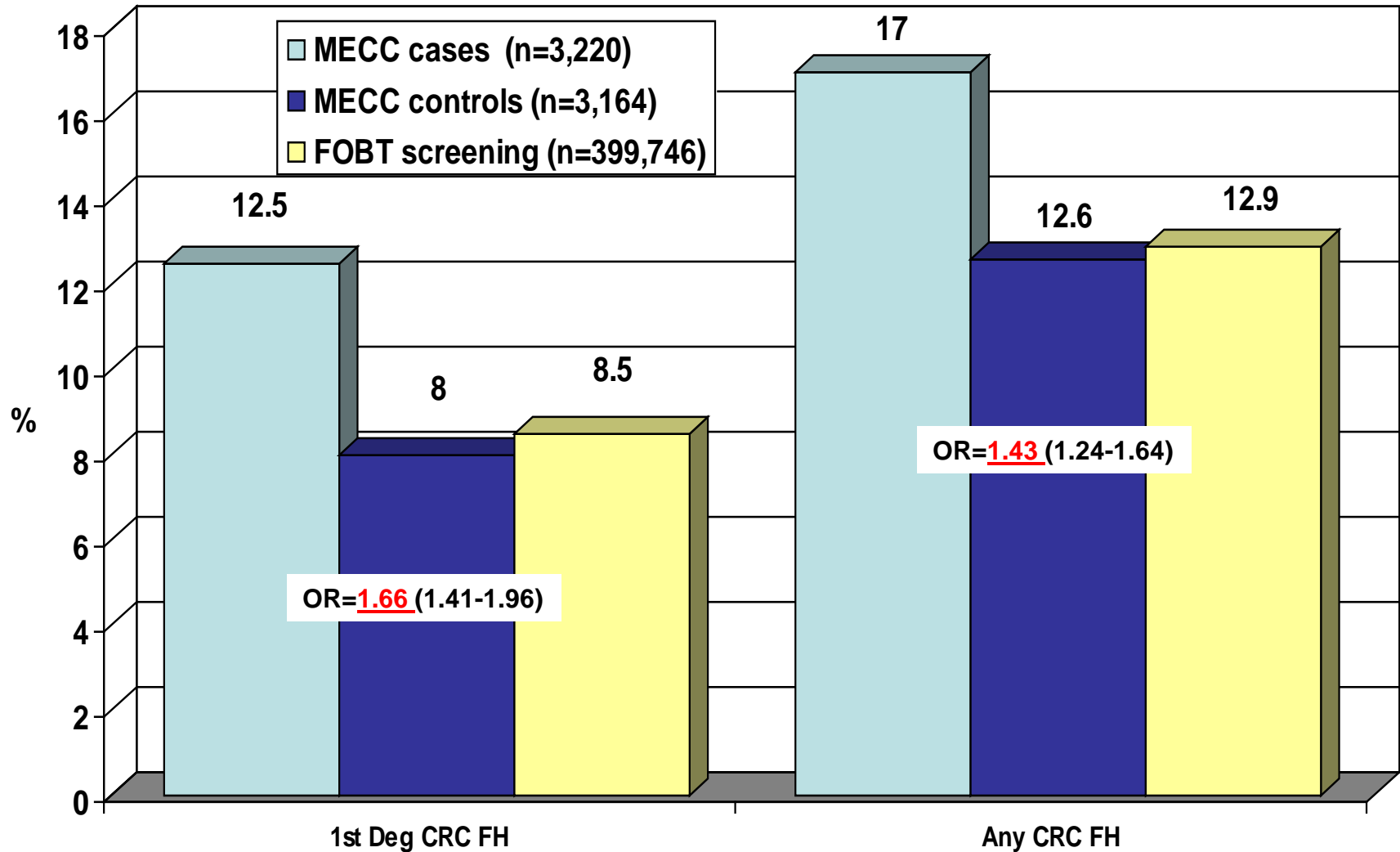
*(Molecular Epidemiology of Colorectal Cancer)*

*(Carmel/Technion- Dr. G. Rennert  
and U. of Michigan/USC- Dr. S. Gruber)*

- Population-based case-control study
- Incident cases of CRC in Northern Israel (1998-2004...-)
- Controls matched for age, gender, neighborhood (clinic)
- 2,100 cases, 2,100 controls in phase I (> 9,500 to date)
- Behavioral/environmental data from **interview** (about 800 questions including food frequency questionnaire)
- **Clinical records** (hospital, pathology, oncology follow-up). Computerized pharmacy and laboratory records.
- **Biosamples**: DNA, sera, frozen lymphocytes, frozen tumor, paraffin blocks

# Family history of CRC reported in Israel

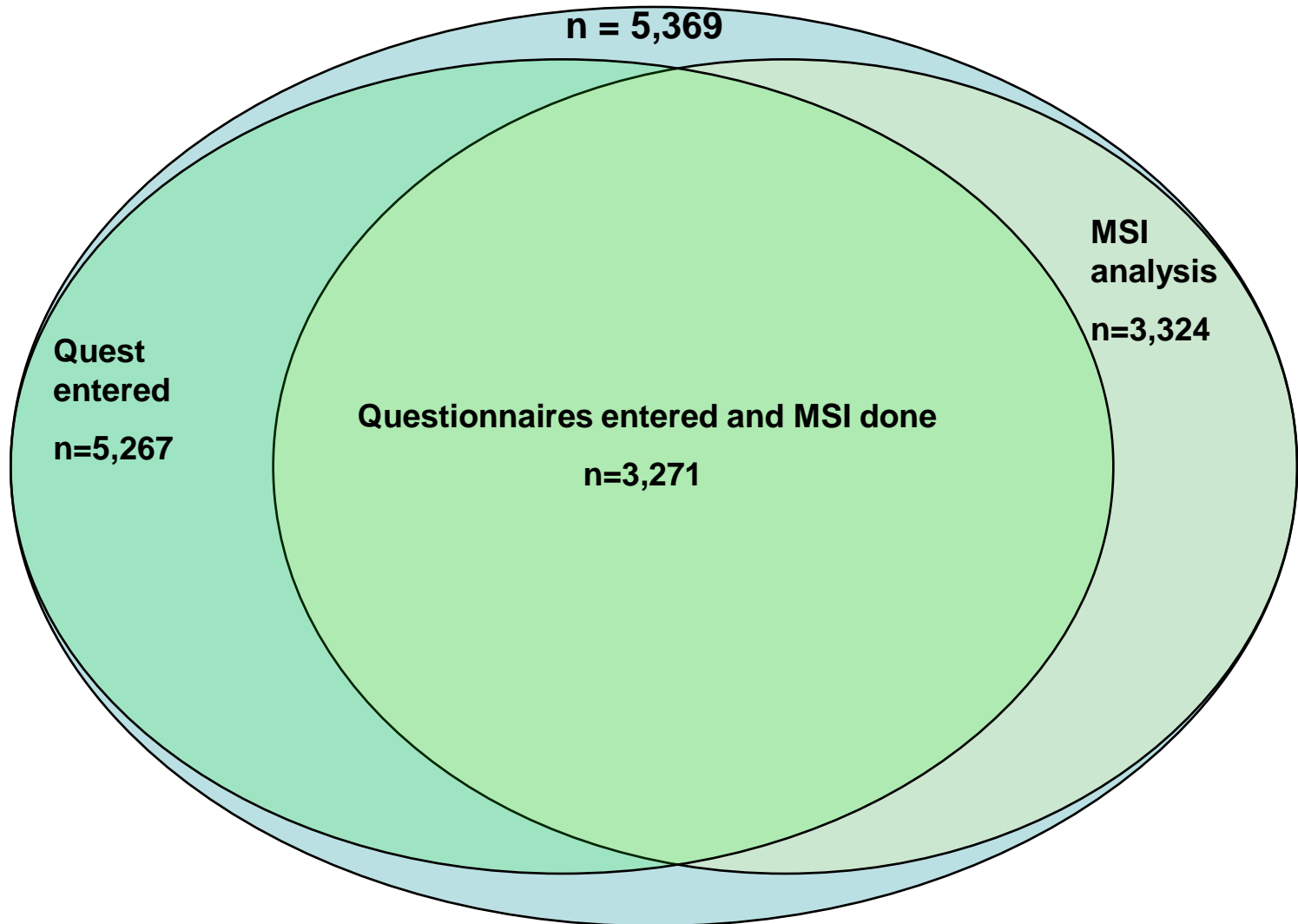
## MECC/FOBT



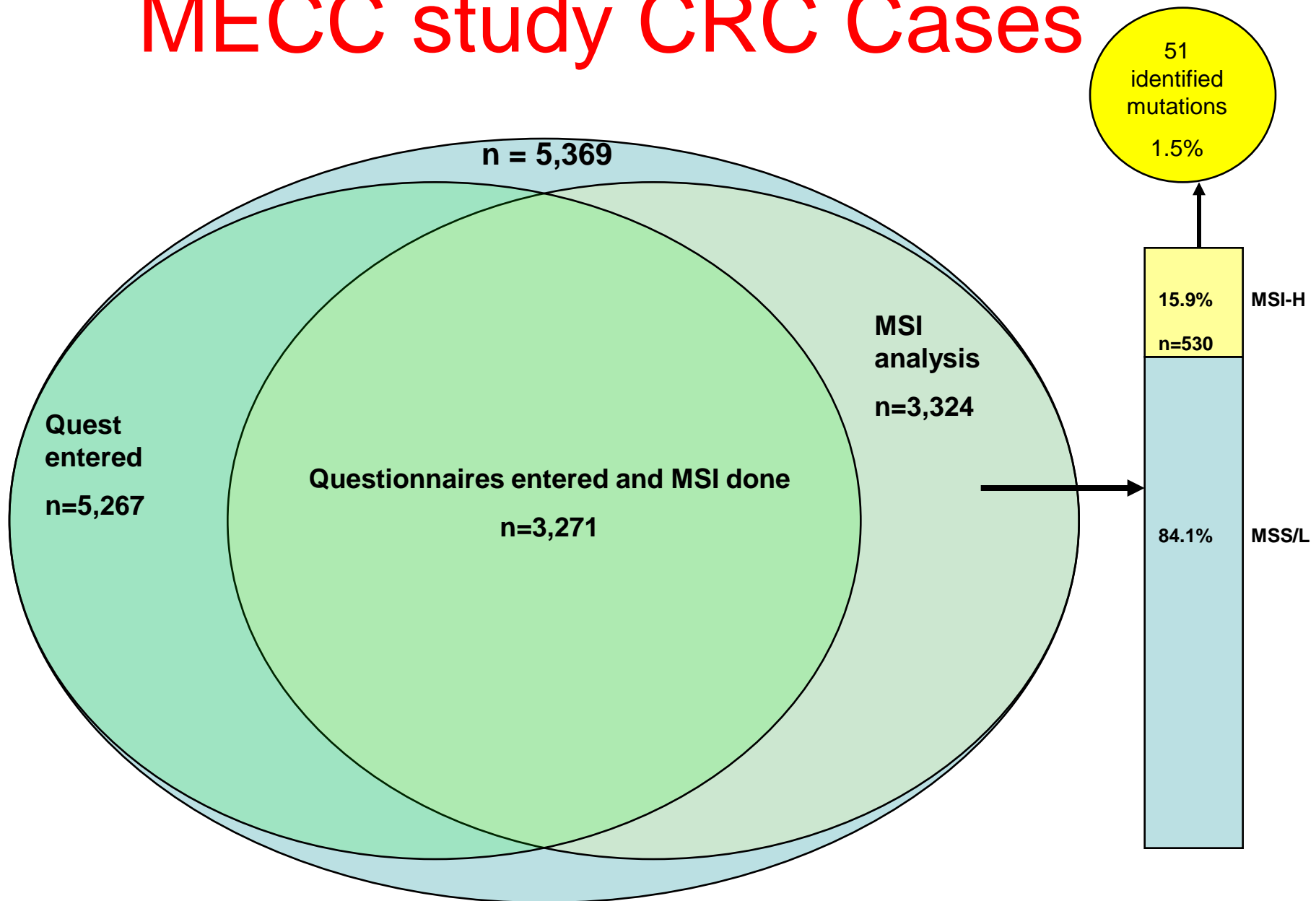
## Number of tests performed for current analysis on MECC cases samples

Tissue Tests	Number	Positive	70,022
MSI- 10 markers (T vs. N)	3,324 x 10 x2	15.9%	
MLH1-IHC (...SEQ)	1,078	24.4%	
MSH2-IHC	1,314	4.4%	
MSH6-IHC	1,151	8.3%	
PMS2 - IHC	221		
KRAS (6)	3,195	39.3%	
BRAF	3,192	7.6%	
PI3K (3)	1,772	9.7%	
EGFR (3)	1,780	0.3%	
<b>Blood Tests</b>			30,085
MSH2-A636P	5,007	0.7% Ash	
MSH6 Exon 9 indels	3,337	0.5% Ash	
APC I1307K	5,054	7.4% All	
MUTYH Y179C/G396D	1,648	6.6% N. Af	
BRCA founders (185delAG, 5382insC, 6174delT)	15,039	1.5% Ash	

# MECC study CRC cases



# MECC study CRC Cases



# Distribution of mutation identified at NICCC

<b>MLH1</b>	# carriers	# families
1411del4	2	1
K618A	2	1
R226X	4	1
1852del	1	1
Ex 2. 208-2A<C	2	1
W666X	1	1
Exon 18 1998G>A	1	1
Ex 15, 2599G>A E867X	1	1
Ex 16 K618A	1	1
<b>MSH6</b>		
Exon 9 del/dup	48	25
Exon 1 116 G-A G35E ?	4	4

<b>MSH2</b>	# carriers	# families
A636P	118	33
Exon 4 704delA K235X	31	10
Q324X	7	2
Exon 9/10 hetero del	1+	>
R389X	27	1
Q158X	9	1
1569delT	1	1
E205X	2	1
I841X	1	1
M592V	2	1
657delAG	2	1
R383X	1	1
E867X	1	1

## **MSH2 A636P (1906G>C) and HNPCC**

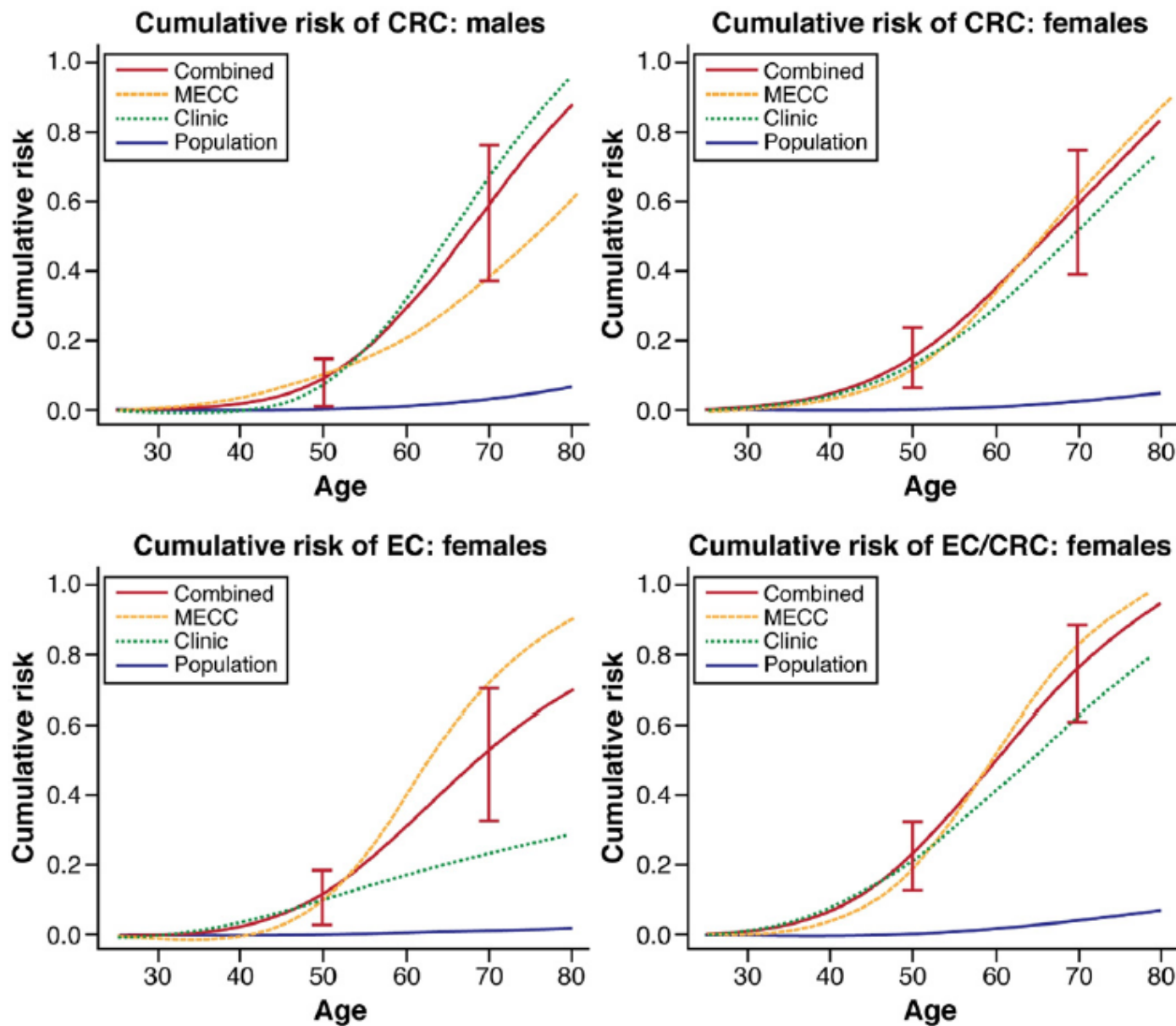
- 24 unrelated **Ashkenazi** families (founder)
- All showed **MSI** in IHC
- **MECC study**: 3/686=**0.44%** (0/159 Sephardi)  
2/75 under age 60, 1/611 over age 60
- Very high rate of endometrial cancer in families



**Table 3:** Age specific and overall hazard ratio for Colorectal and Endometrial Cancers for A636P mutation carriers.

	Colorectal Cancer (Males)			Colorectal Cancer (Females)		
Age	Hazard Ratio <i>A636P</i> Carriers (95% CI) Combined	Hazard Ratio <i>A636P</i> Carriers (95% CI) MECC	Hazard Ratio <i>A636P</i> Carriers (95% CI) CHS	Hazard Ratio <i>A636P</i> Carriers (95% CI) Combined	Hazard Ratio <i>A636P</i> Carriers (95% CI) MECC	Hazard Ratio <i>A636P</i> Carriers (95% CI) CHS
20-49	39.8 (17.3-91.9)	55.4 (19.6-156.7)	19.9 (4.8-81.9)	65.9 (36.5-119.0)	44.8 (18.2-110.3)	57.7 (24.9-133.7)
50-79	29.7 (17.1-51.6)	12.3 (4.2-36.0)	40.8 (21.5-77.4)	31.8 (18.3-55.2)	37.2 (16.7-82.9)	24.7 (11.0-55.2)
Overall HR	31.8 (19.9-51.0)	20.3 (9.4-44.1)	34.8 (19.3-62.8)	41.8 (27.4-64.0)	40.2 (21.6-74.7)	34.2 (18.5-63.2)

	Endometrial Cancer (Females)			Colorectal and Endometrial Cancer (Females)		
Age	Hazard Ratio <i>A636P</i> Carriers (95% CI) Combined	Hazard Ratio <i>A636P</i> Carriers (95% CI) MECC	Hazard Ratio <i>A636P</i> Carriers (95% CI) CHS	Hazard Ratio <i>A636P</i> Carriers (95% CI) Combined	Hazard Ratio <i>A636P</i> Carriers (95% CI) MECC	Hazard Ratio <i>A636P</i> Carriers (95% CI) CHS
20-49	88.8 (43.0-183.5)	33.3 (7.3-152.8)	97.3 (39.1-242.3)	67.4 (41.5-109.5)	40.9 (19.0-88.4)	69.2 (36.4-131.5)
50-79	58.1 (32.9-102.7)	114.8 (58.0-227.4)	11.6 (2.5-53.9)	35.8 (22.7-56.4)	50.0 (28.0-89.2)	20.7 (9.7-43.9)
Overall HR	66.7 (41.7-106.7)	83.3 (45.4-153.1)	33.0 (14.7-74.1)	46.0 (32.4-65.4)	46.4 (28.8-74.8)	35.6 (20.9-60.9)



**Figure 1.** Cumulative risk of CRC and EC by sex in A636P mutation carriers compared with the Israeli Ashkenazi population (men, *top left*; women, *top right*; EC in women, *bottom left*; and either CRC or EC in women, *bottom right*) in MSH2 carriers and the population. The 95% CIs are reported at ages 50 and 70 years.

## Original Article

# Characterization of two Ashkenazi Jewish founder mutations in *MSH6* gene causing Lynch syndrome

Raskin et al.

Table 2. Risk of colorectal and endometrial cancers among *MSH6* exon 9 indel mutation carriers in an Ashkenazi Jewish population

Mutation	Cases	Controls	OR	95%CI	p-Value
CRC					
c.3984_3987dupGTCA	8/2685 (0.3%)	1/3310 (0.03%)	9.9	1.2–78.9	0.0079
c.3962_3965delCAAG	3/2685 (0.1%)	0/3310	∞	∞	0.0546
<i>MSH6</i> exon 9 dup or del	11/2685 (0.4%)	1/3310 (0.03%)	13.6	1.8–105.1	0.0011
EnCa <sup>a</sup>					
c.3984_3987dupGTCA	2/337 (0.6%)	1/3310 (0.03%)	19.6	1.8–217.2	0.0006
c.3962_3965delCAAG	2/337 (0.6%)	0/3310	∞	∞	<0.0001
<i>MSH6</i> exon 9 dup or del	4/337 (1.2%)	1/3310 (0.03%)	39.3	4.4–352.5	<0.0001

CRC, Colorectal cancer; EnCa, endometrial cancer.

<sup>a</sup>EnCa risk was estimated from MSKCC hospital-based series.

# MECC – MSI-H cases

Tissue Tests	MSI-H tumors	MSI-L/MSS tumors
Family history of CRC in 1 <sup>st</sup> degree relative	18.9%	15.9%
Any Family history of CRC	24.3%	21.3%
Fulfillment of Amsterdam Criteria (n=40)	3.9% (20)	0.7% (20)
Amsterdam 3 out of 4	4.3%	2.8%
Amsterdam 2 out of 4	2.3%	1.4%
Any Amsterdam-like	10.5%	4.9%
MLH1 IHC negative (n=249)	48.7%	9.0%
MSH2 IHC negative (n=54)	11.4%	0.6%
MSH6 IHC negative (n=94)	18.0%	3.0%
MSH2- A636P (n=12)	12	0
MSH2 – Ex 4 L245X (n=10)	10	0
MLH1/MSH2 – other mutations (n=14)	14	0
MSH6 Exon 9 indels (n=15)	10	5

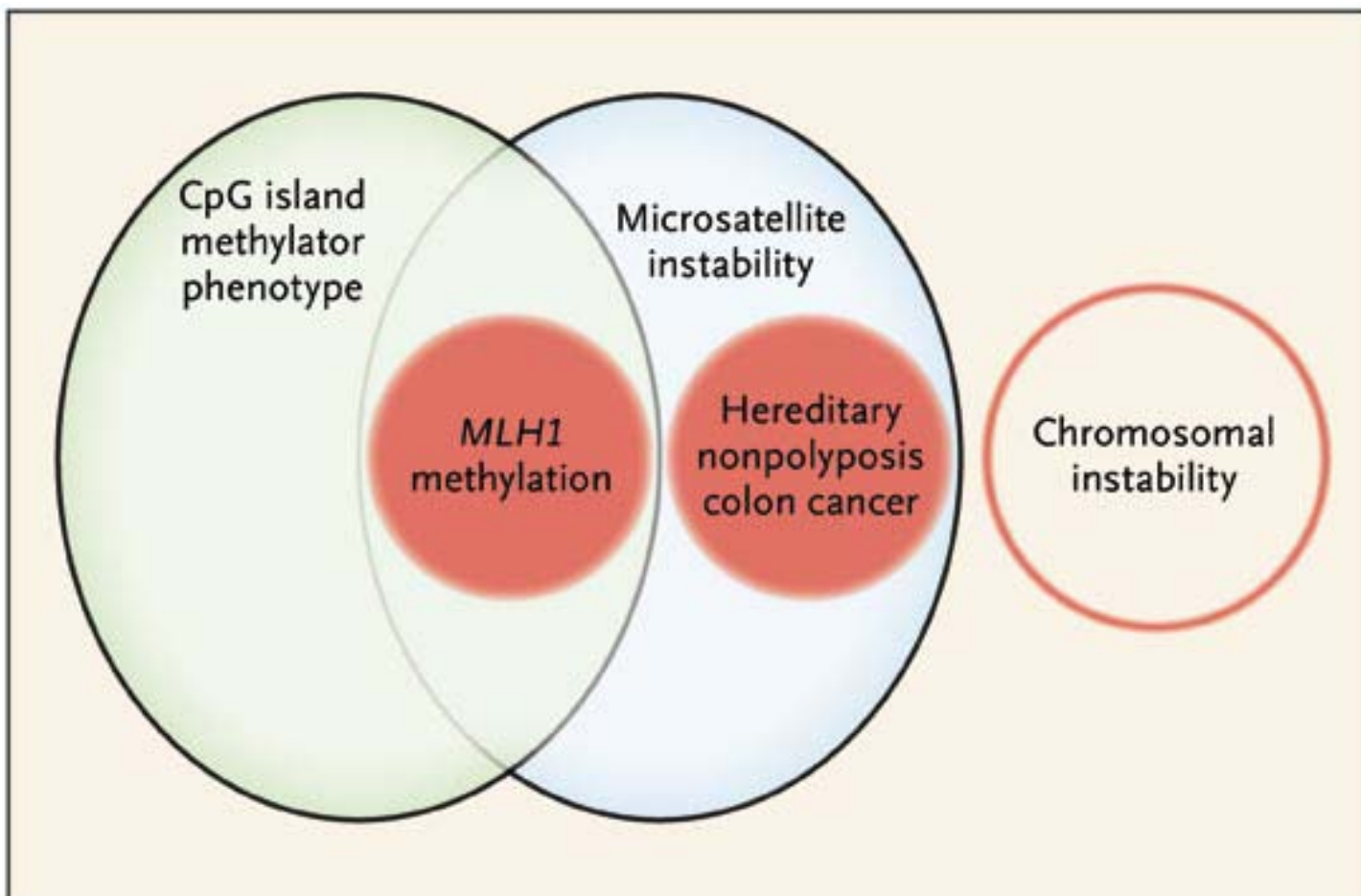
# MECC – MSI-H cases

Tissue Tests	BAT25+BAT26 instable	No BAT25 and BAT26
Family history of CRC in 1 <sup>st</sup> degree relative	24.0%	16.9%
Any Family history of CRC	27.9%	22.9%
Fulfillment of Amsterdam Criteria (n=40)	48.4%	17.4%
Amsterdam 3 out of 4	35.5%	54.8%
Amsterdam 2 out of 4	16.1%	27.8%
MLH1 IHC negative (n=249)	67.2%	9.6%
MSH2 IHC negative (n=54)	17.8%	0.6%
MSH6 IHC negative (n=94)	78.0%	96.5%
Any mutation	13.7%	0.2%
MSH2- A636P (n=12)	9	0
MSH2 – Ex 4 L245X (n=10)	8	0
MLH1/MSH2 – other mutations (n=14)	2	2
MSH6 Exon 9 indels (n=15)	7	3

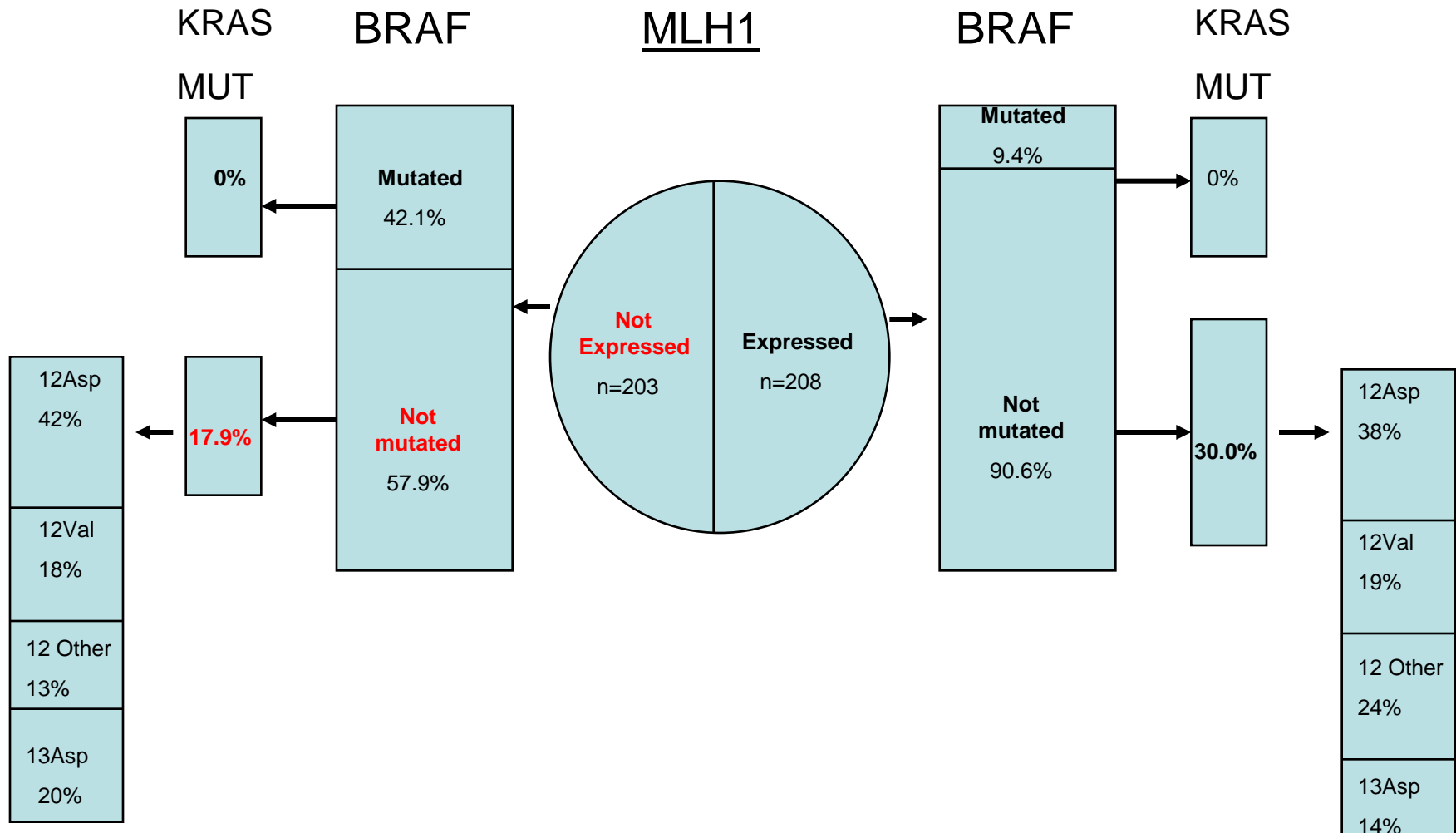
## Tissue markers in carriers of founder mutations

	<b>MSH2 A636P</b>	<b>MSH2 L245X</b>	<b>MSH6 InDels</b>
MLH1 expression	100%	90%	70%
MSH2 expression	11%	0	100%
MSH6 expression	11%	10%	55%
BRAF	11%	0	12%
KRAS	30%	22%	14%
PI3K	0	11%	38%

## Genetic Instability Pathways That Drive Colon Neoplasias

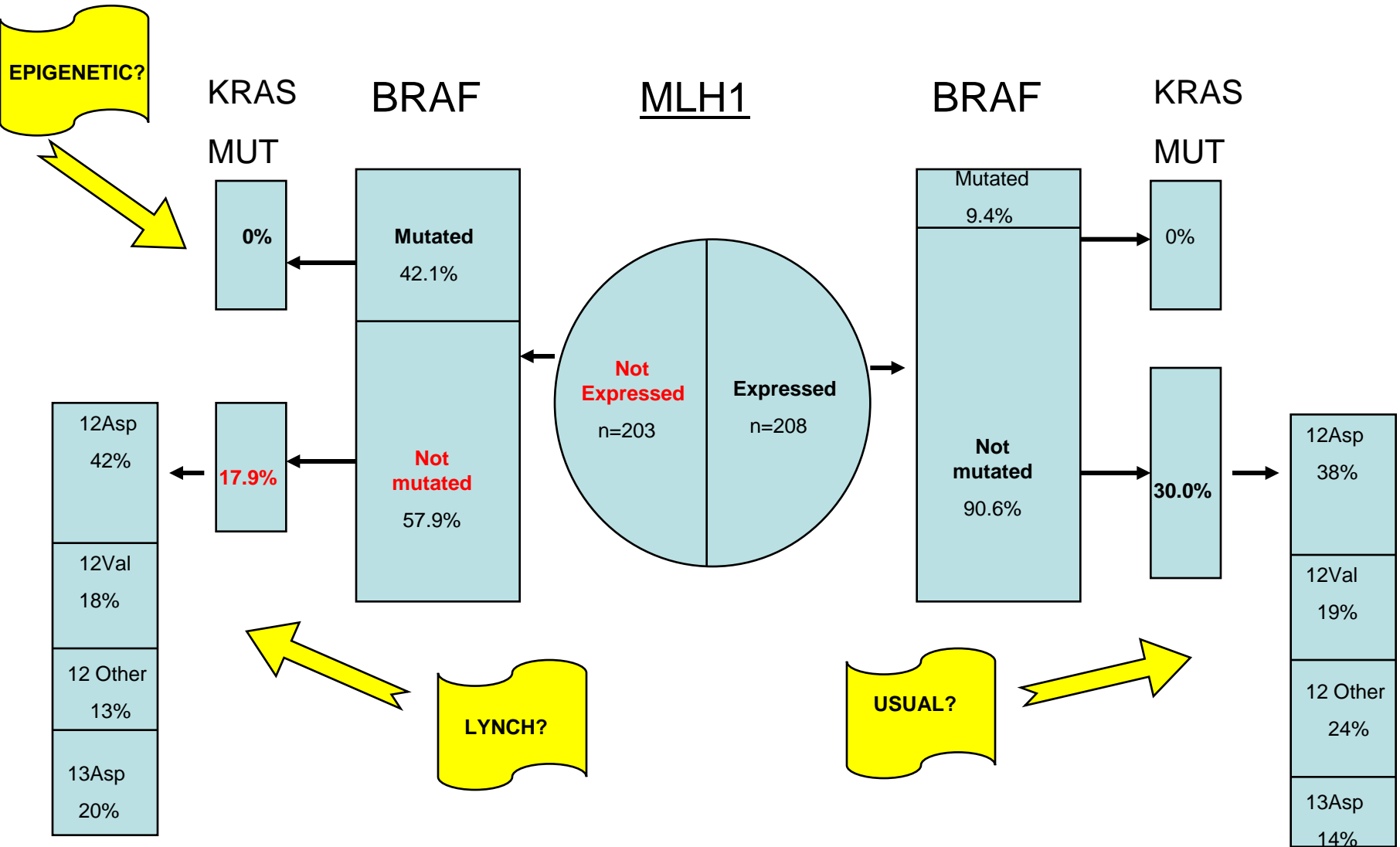


# MLH1/BRAF/KRAS in MSI-H tumors

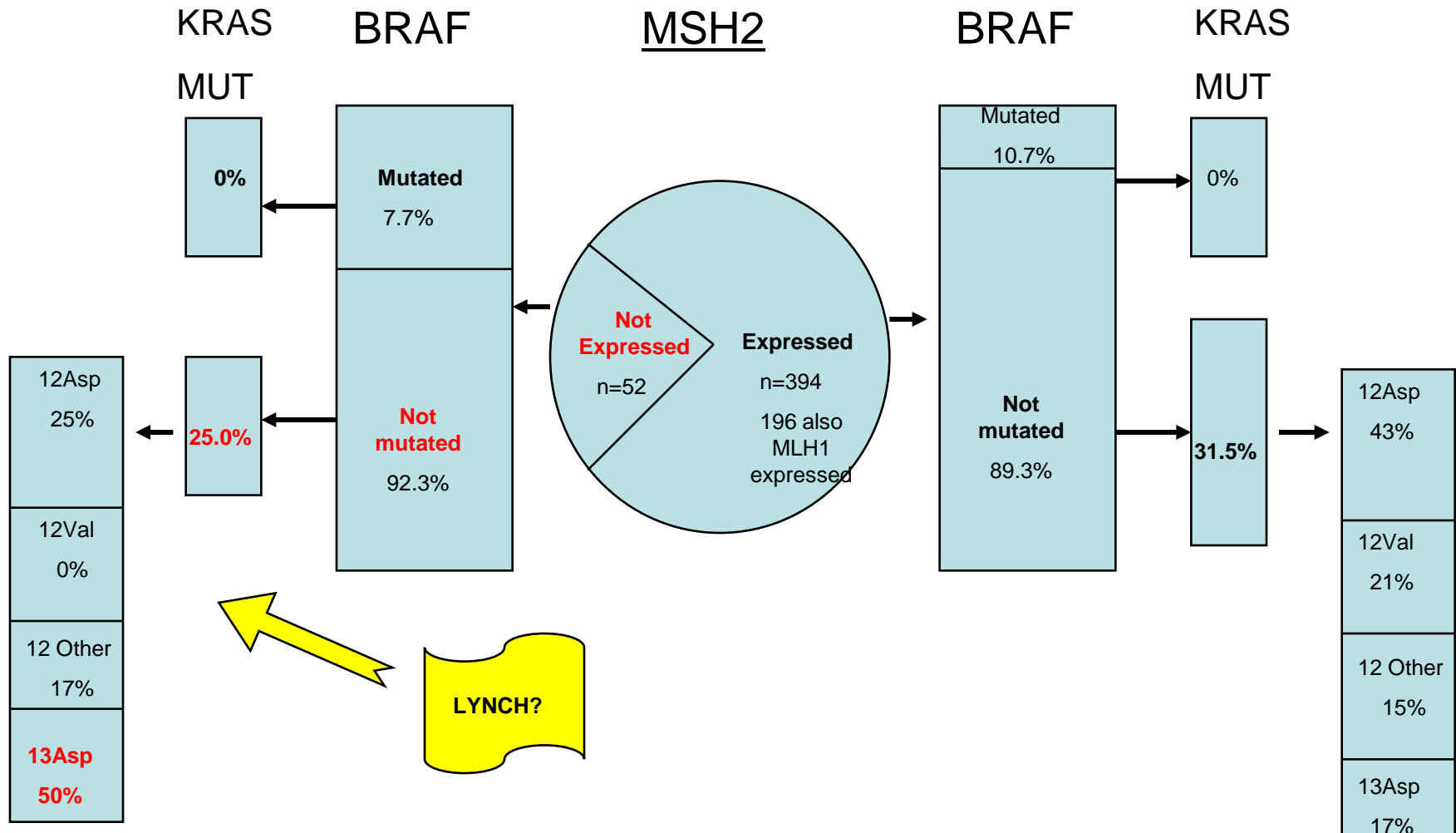




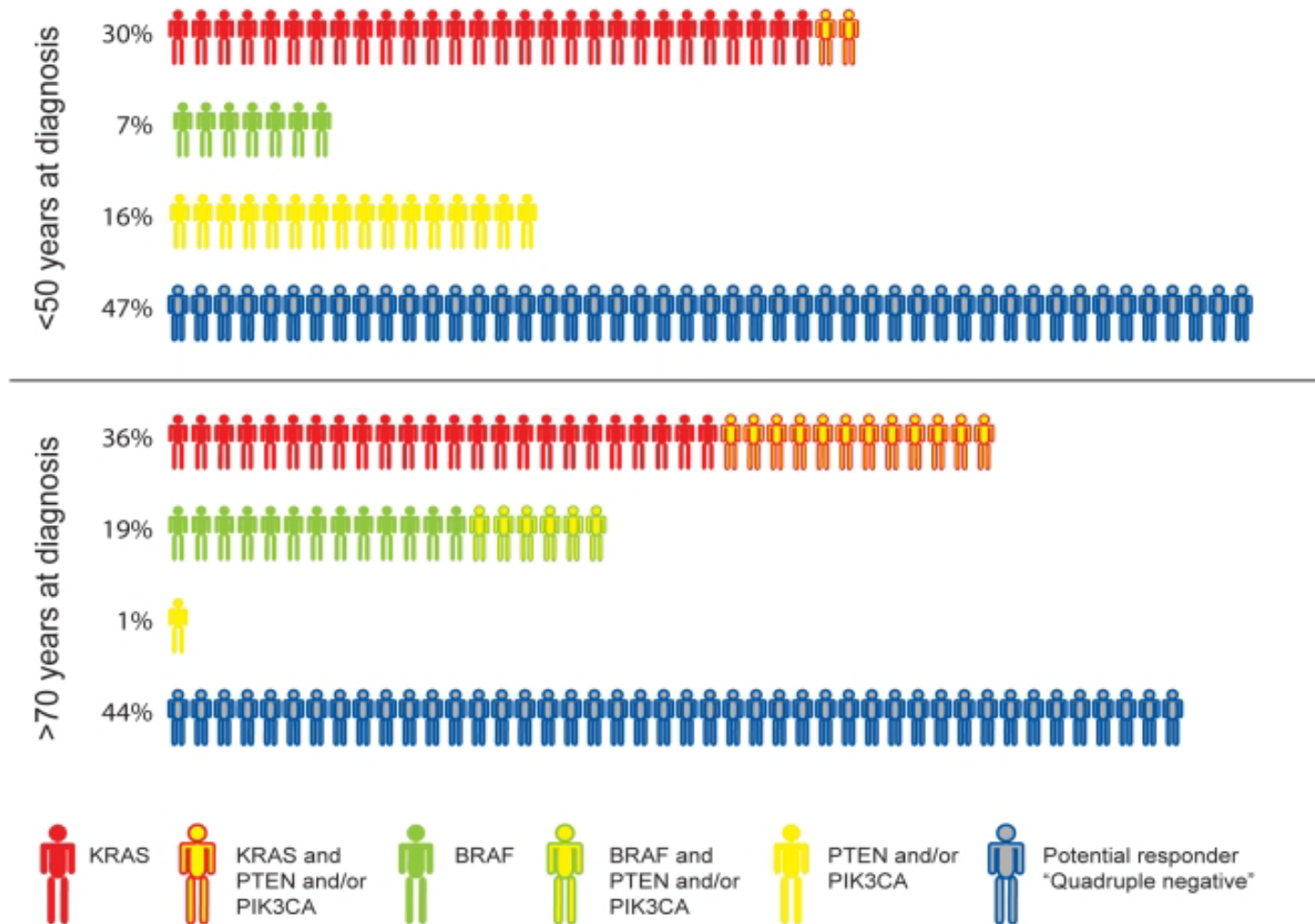
# MLH1/BRAF/KRAS in MSI-H tumors



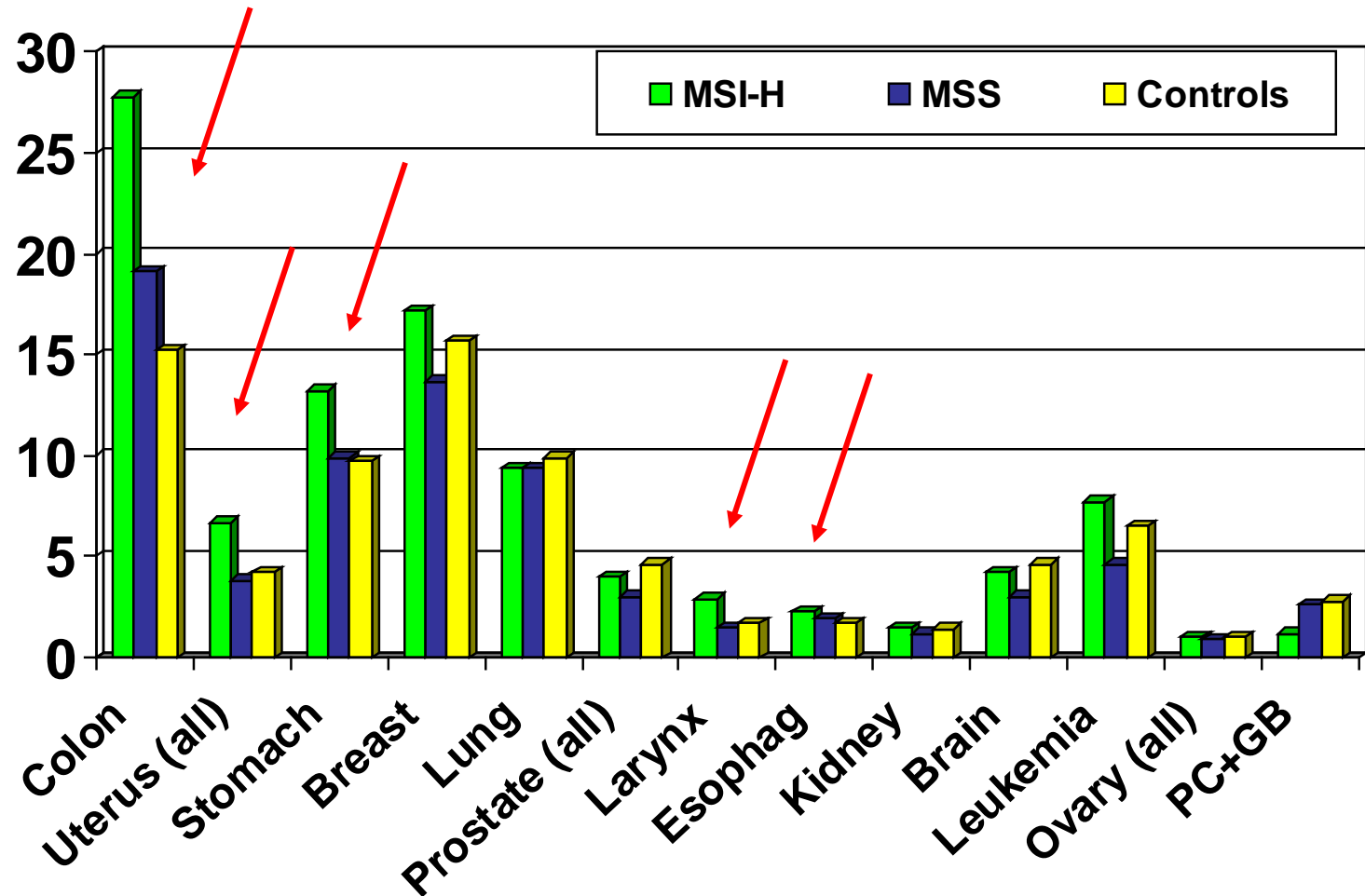
# MSH2/BRAF/KRAS in MSI-H tumors



# Graphic representation of patients with hypothesized response to EGFR-targeted therapy.



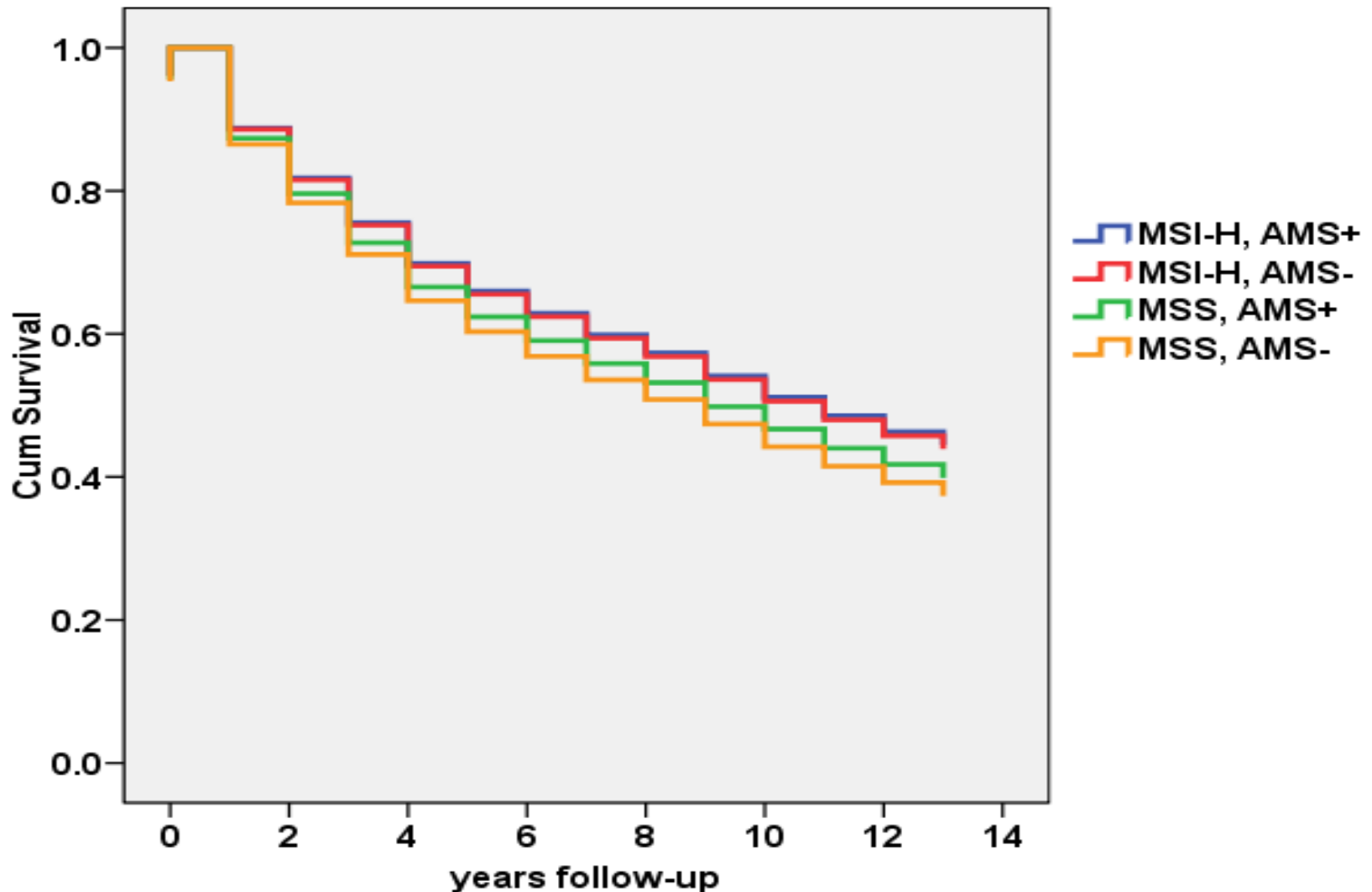
# Frequency of tumors reported in family members of MECC cases



# Clinical pathological data

	MSI-H	MSS	Amsterdam positive	Synd X (AMS/MSS)	Identified mutations
Tumor in Rt colon	62.2%	34.3%	40.9%	31.5%	51.1%
Mucinous features	55.1%	34.1%	37.0%	27.6%	55.3%
Age at diagnosis	69.1	69.4	65.2	65.4	61.1

# Survival of MECC cases, by MSI status and Amsterdam criteria



# How should we handle suspicion of Lynch Syndrome in Israel?

1. Test for founders when available (liberal)
2. Test for MSI (also other added values). Choose best sample in family (site, age, histology, availability of normal tissue).
3. Test MSI-Hs for IHC expression of relevant genes (difficulties)
4. Exclude non-expressed MLH1 if PMS2 also non-expressed and BRAF is mutated. Exclude after MLPA.
5. Sequence MSI-H cases with no relevant gene expression after exclusions for methylation and founders.

# Acknowledgement

## HAIFA

### Management/Analysis team:

Hedy S Rennert

Dr. Mila Pinchev

### Lab team:

Dr. Flavio Lejbkowitz

Dr. Miriam Luria

Dr. Edmond Sabo

Dr. Meira Frank

Dr. Vered Friedman

Dr. Ilana Cohen

Dr. Shiri Kelt

Dr. Esti Liani

### Clinical team:

Dr. Kati Shulman

Dr. Anath Flugelman

Dr. Riad Hadad

## USA

Dr. Stephen B Gruber

Dr. Joel Greenson

Dr. Leon Raskin

Dr. Laora Rozek

And to many many other physicians,  
technicians, interviewers, and patients



***Thank you***