Pathogenic somatic mutation (SM) of mismatch repair (MMR) genes and associations with microsatellite instability (MSI), tumor mutational burden (TMB) and SM in other DNA repair pathways in 24,223 tumor genomic profiles

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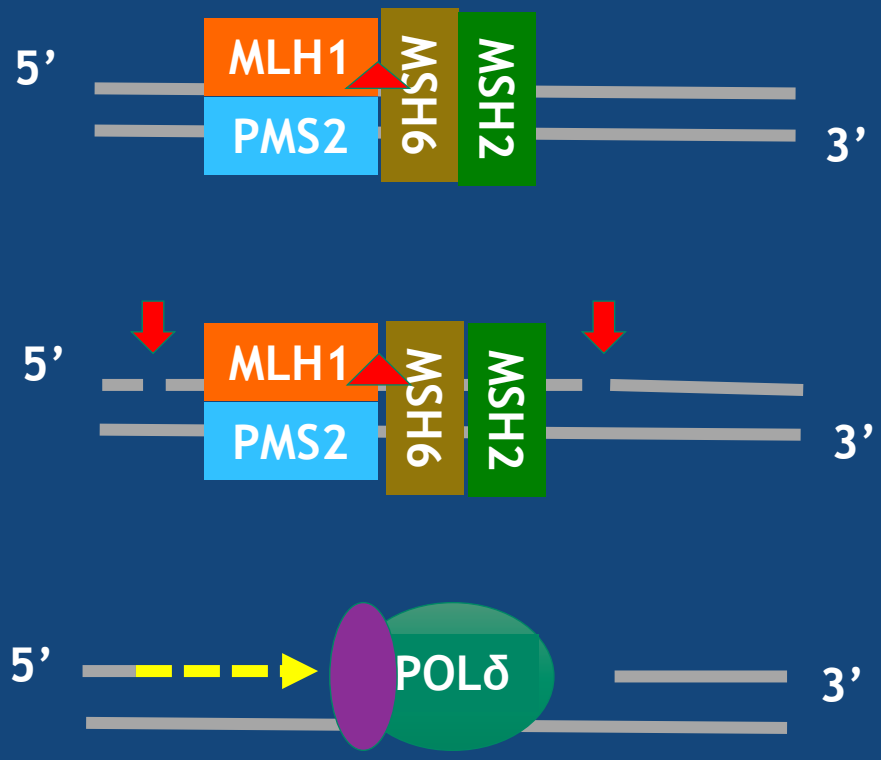
Mismatch repair (MMR) and Lynch syndrome (LS)

Mismatch repair



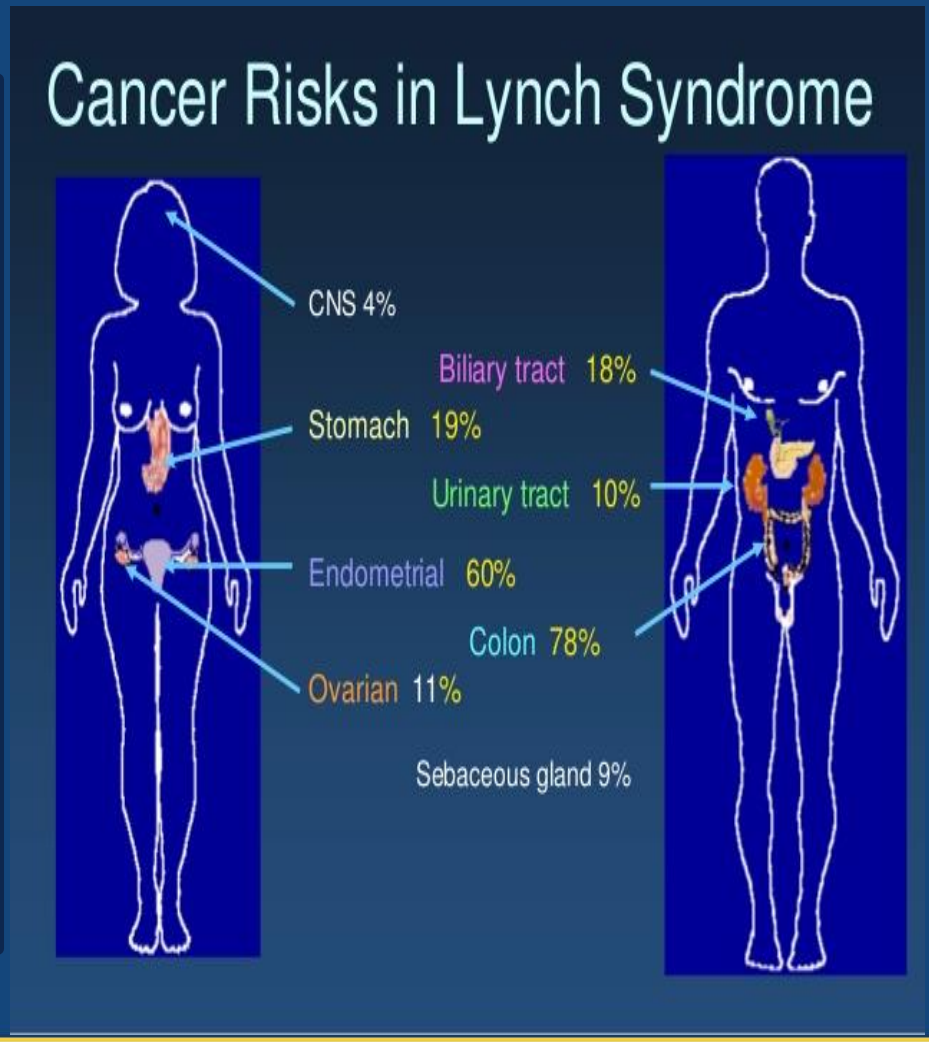
TAKEAWAYS

MLH1, MSH2, MSH6, PMS2 are the clinically relevant MMR genes

MLH1/PMS2 & MSH2/MSH6 function as heterodimers

Deficient MMR (dMMR) leads to microsatellite instability

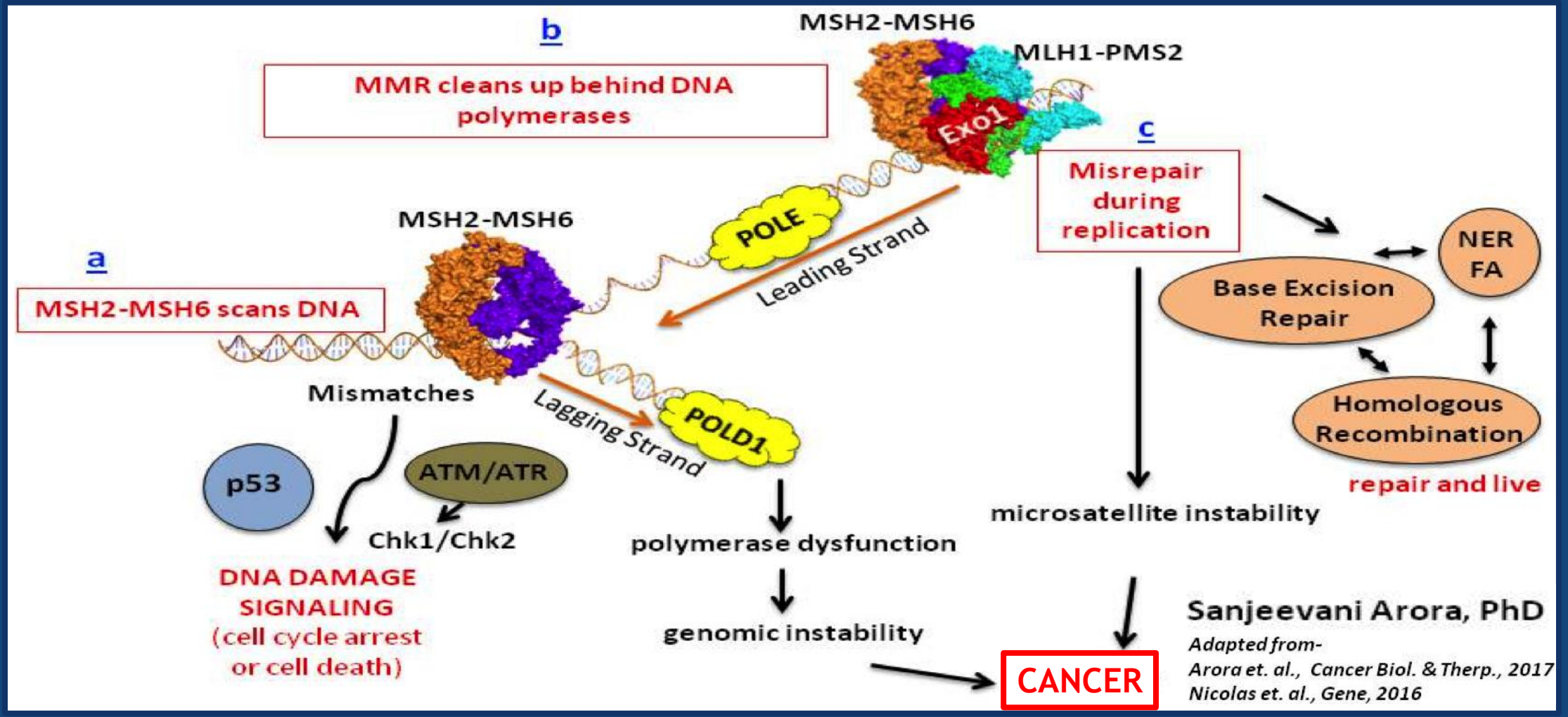
LS is the autosomal dominant inheritance of a MMR gene mutation



Interactions between DNA repair pathways

DNA REPAIR PATH-WAYS

1-MMR
2-HR
3-BER
4-NER
5-NHEJ
6-POL

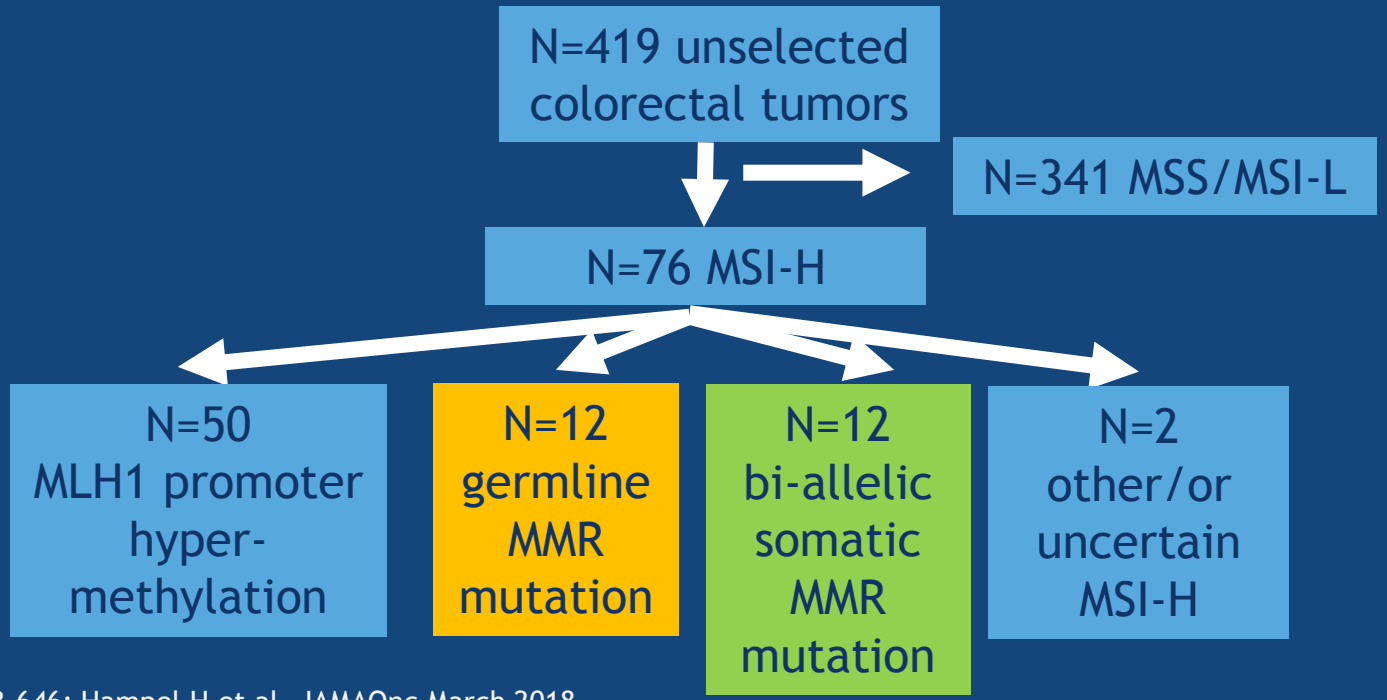


Mono- (mSM) and bi-allelic (bSM) somatic mutations causing deficient MMR (dMMR)

- bSM in MLH1, MSH2, MSH6 or PMS2 is a clinically relevant cause of dMMR
- Primary cause of tumor dMMR (1.9%) after germline MMR mutation (2.8%) and MLH1 promoter methylation (11.9%)

JAMA Oncology | Original Investigation

Assessment of Tumor Sequencing as a Replacement for Lynch Syndrome Screening and Current Molecular Tests for Patients With Colorectal Cancer



Mensenkamp AR et al. Gastroenterology. 2014 Mar;146(3):643-646; Hampel H et al. JAMAOnc March 2018.

dMMR is found in histologically diverse tumors

Tumor type	MSI-H rate (%)	Sample size
Uterine	14.1	39/277
Small Bowel	8.6	6/70
Prostate	6.2	11/178
Colorectal	3.5	42/1185
Cancer of Unknown Primary	2.7	22/815
Hepatobiliary	2.3	9/389
Gastroesophageal	1.5	6/400
Neuroendocrine	0.2	1/431
Pancreas	0.2	1/459
NSCLC	0.2	5/2112
Breast	0.1	2/1459

Hall MJ et al. JCO 34, no. 15_suppl (May 20 2016) 1523-1523.

- MSI-H was identified in nearly every tumor histology, many non-Lynch syndrome spectrum tumors.
- Unclear how MSI related to high tumor mutational burden, but mutational patterns seen.
- Could MSI and/or MMR mutations result from mutations in non-MMR DNA repair pathways?

Study Objectives

- Determine the frequency of mSM and bSM in the MMR genes (MLH1, MSH2, MSH6, PMS2) in a large sample of histologically diverse tumors undergoing commercial tumor genomic testing.

- Associate these with the MSI-H phenotype, TMB, and SM in other DNA repair pathways.

- Associate these with tumor histology and CRC sidedness (L vs R).

Methods

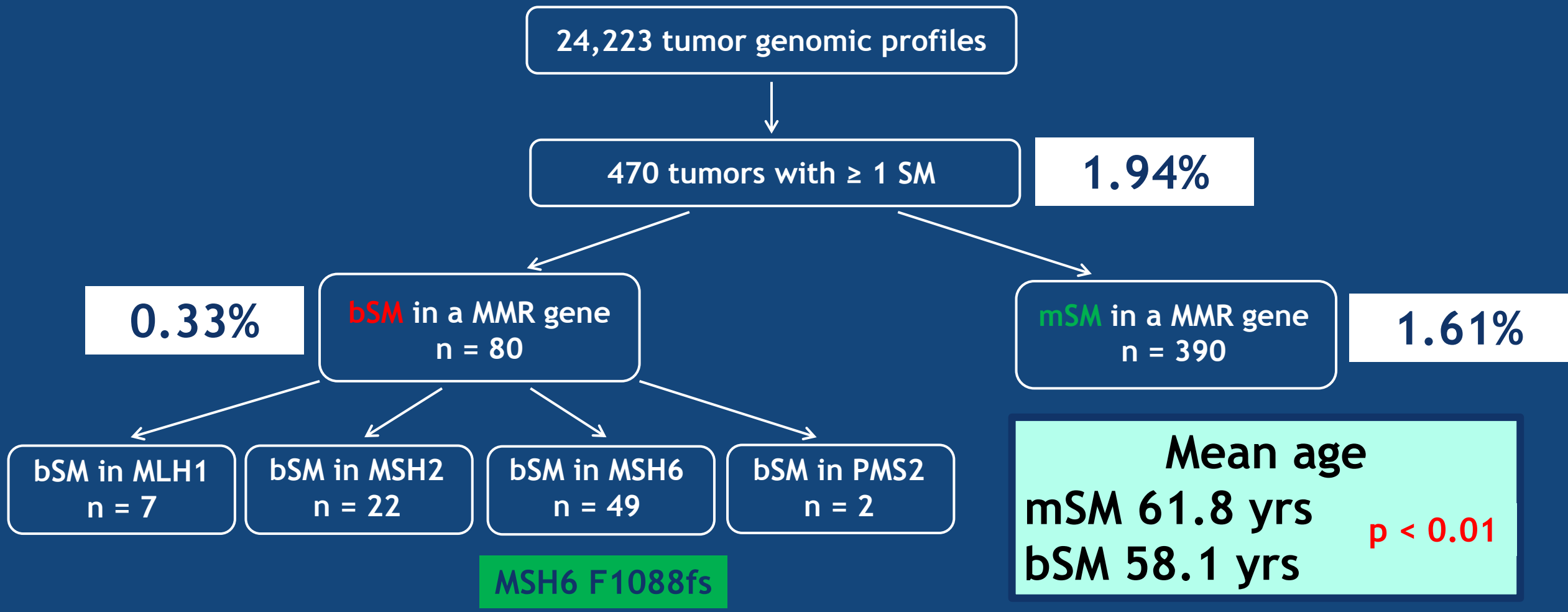
Sample for analyses

- The Caris Life Sciences database was queried for tumors with ≥ 1 SM of an MMR gene (N= 24,223). Convenience sample of tumors undergoing tumor genomic testing.
- Tumors tested with a NGS multi-gene panel (Illumina NextSeq 592 gene panel).

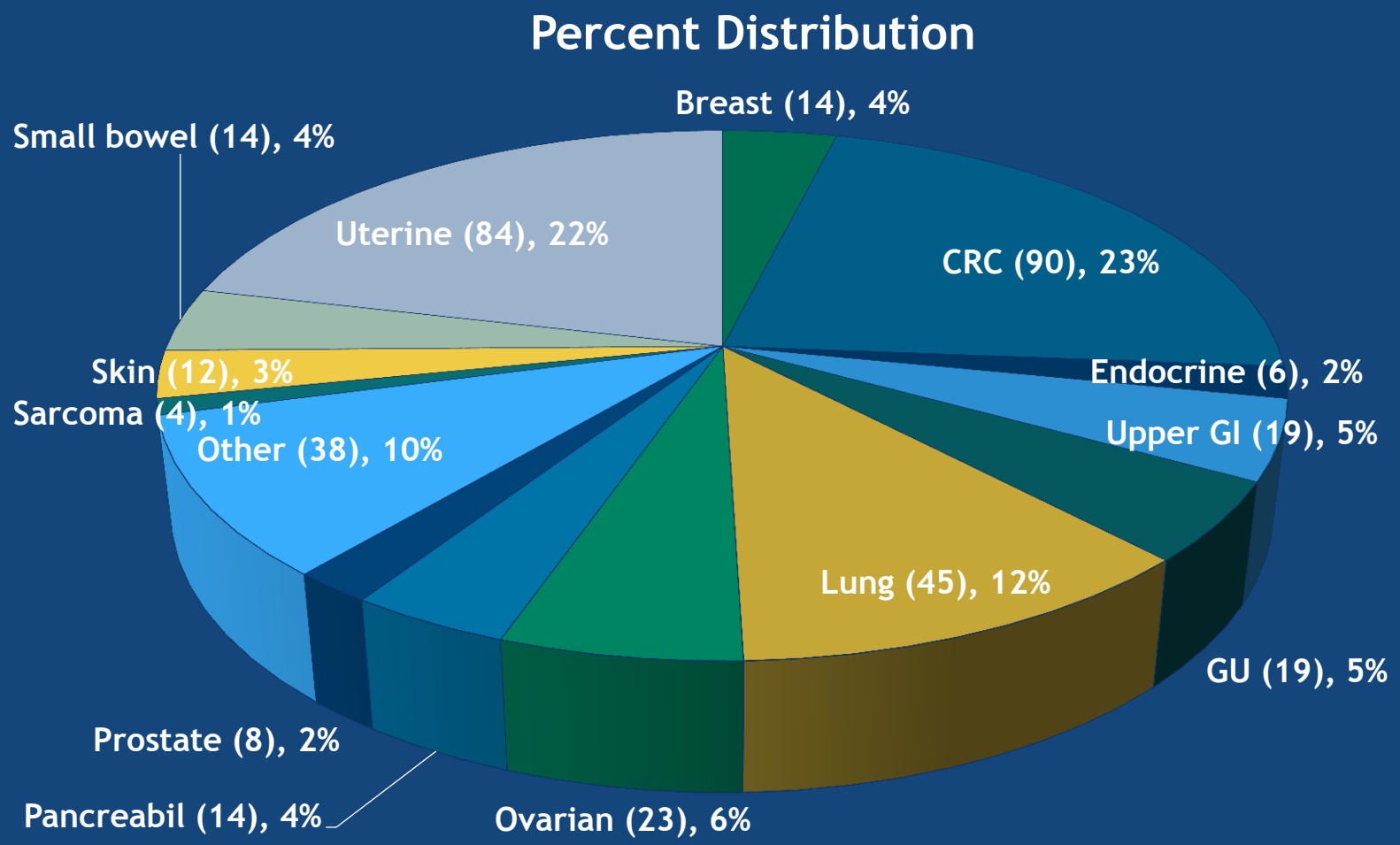
Variables of interest and statistical approach

- Likely pathogenic/pathogenic mSM or bSM in an MMR gene (MLH1, MSH2, MSH6, PMS2).
- MSI, TMB (high ≥17 mut/Mb), tumor histology/location, non-MMR DNA repair pathway mutation.
- Statistics: Associations tested by Fisher's exact test and logistic regression.

Prevalence and frequency of bSM and mSM



Frequency of MMR mSM by tumor histology

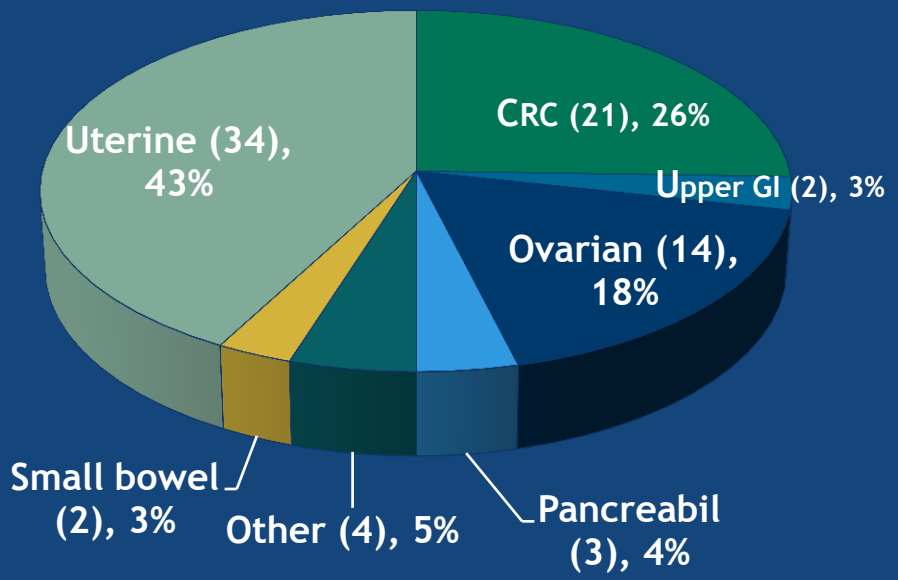


Tumor Type (N), %

- Breast (14), 4%
- CRC (90), 23%
- Endocrine (6), 2%
- Upper GI (19), 5%
- GU (19), 5%
- Lung (45), 12%
- Ovarian (23), 6%
- Pancreabil (14), 4%
- Prostate (8), 2%
- Other (38), 10%
- Sarcoma (4), 1%
- Skin (12), 3%
- Small bowel (14), 4%
- Uterine (84), 22%

Frequency of MMR bSM by tumor histology

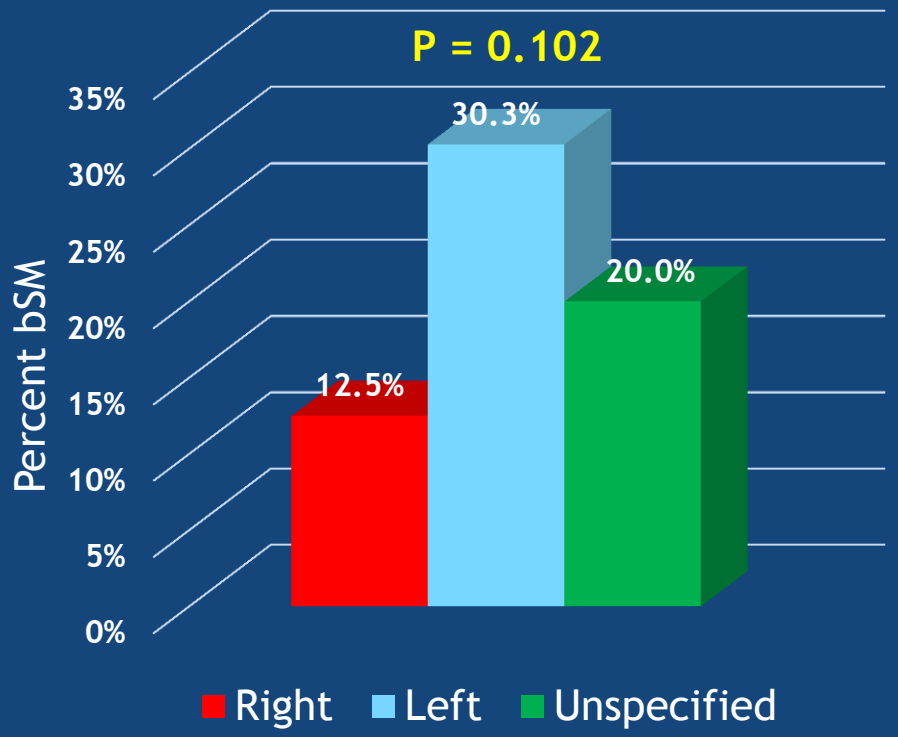
Percent Distribution



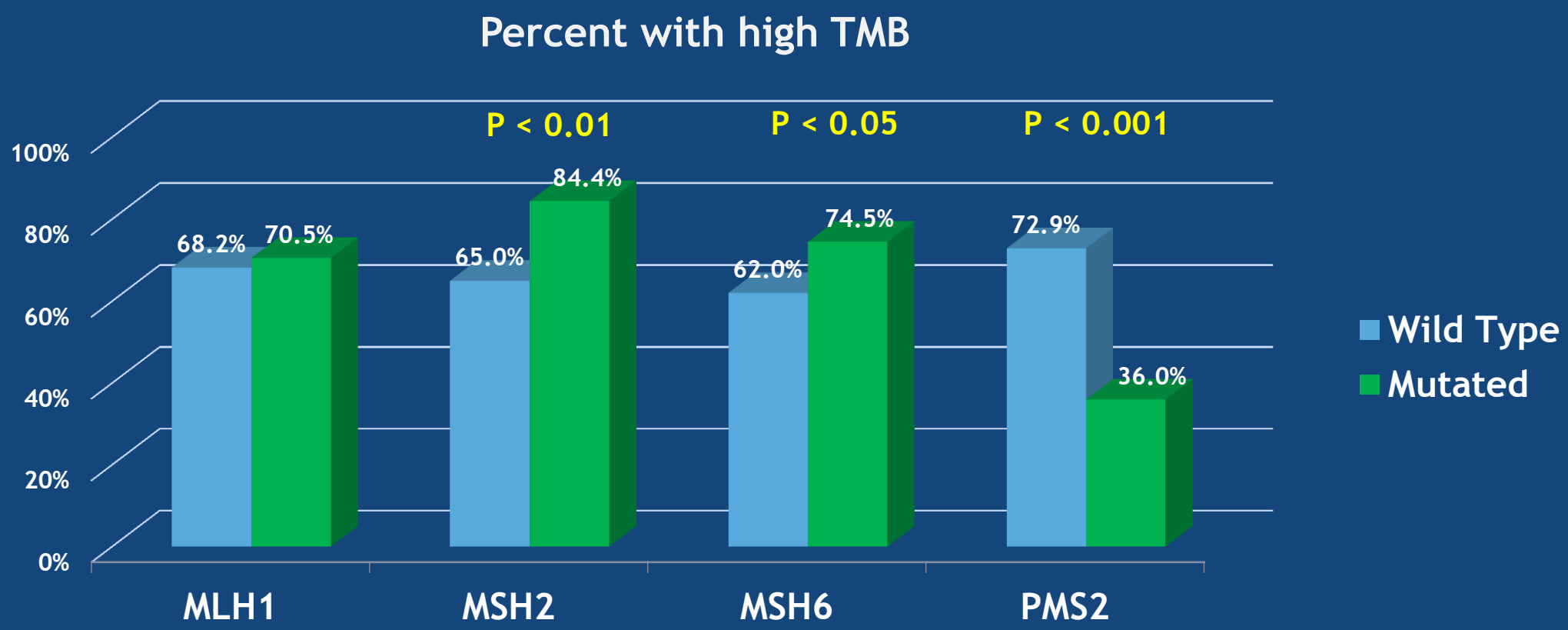
Tumor Type (N), %

- CRC (21), 26%
- Upper GI (2), 3%
- Ovarian (14), 18%
- Pancreabil (3), 4%
- Other (4), 5%
- Small bowel (2), 3%
- Uterine (34), 43%

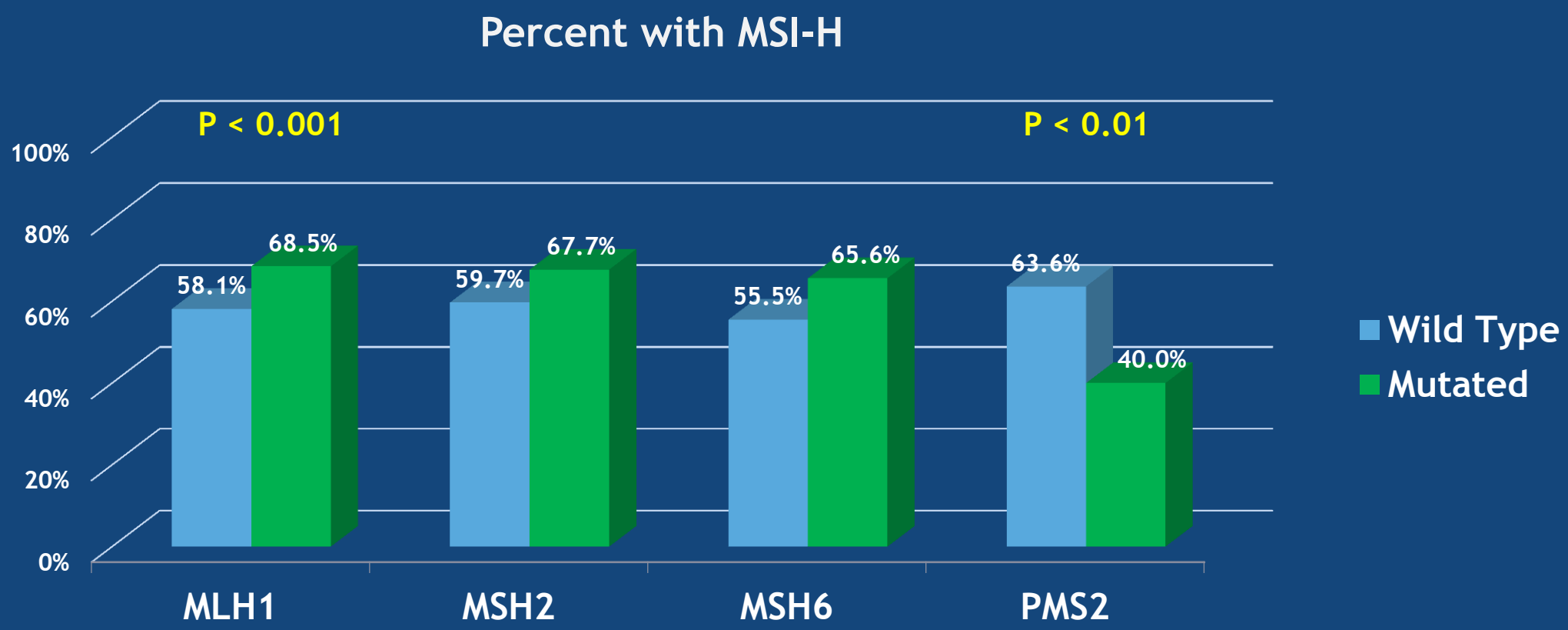
Percent bSM by CRC Site



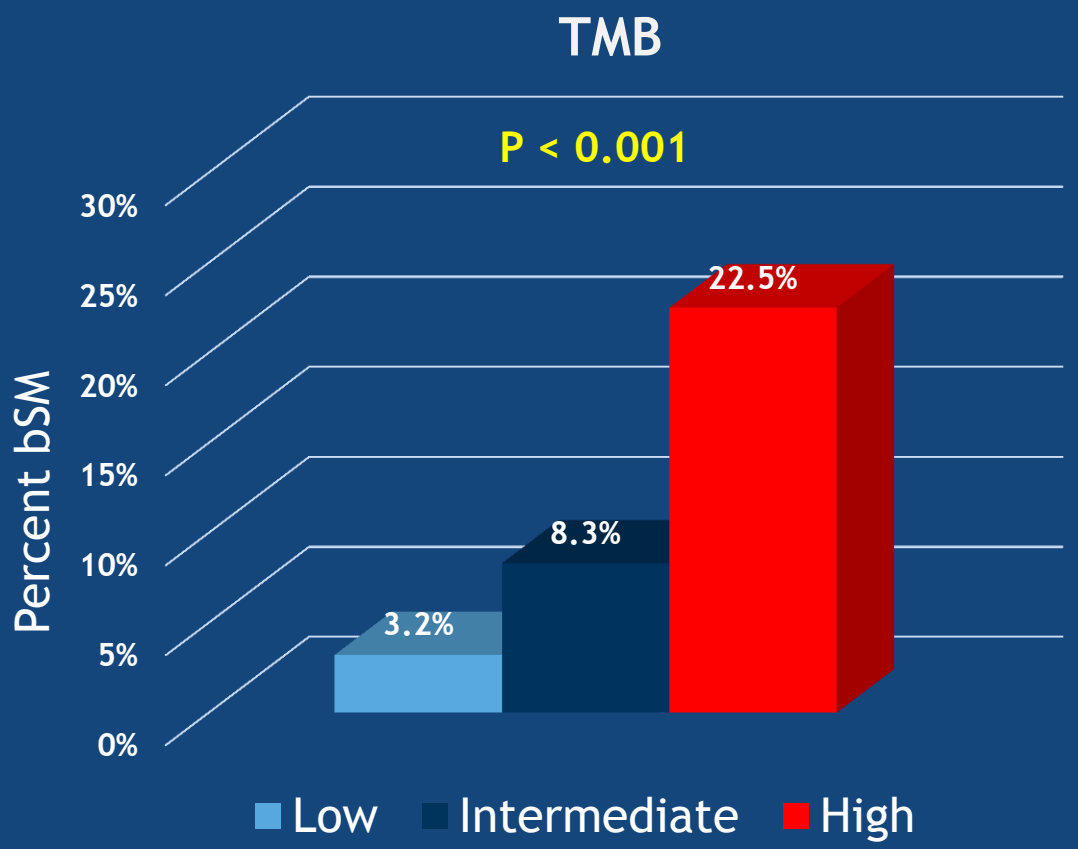
Association of MMR mSM with high TMB

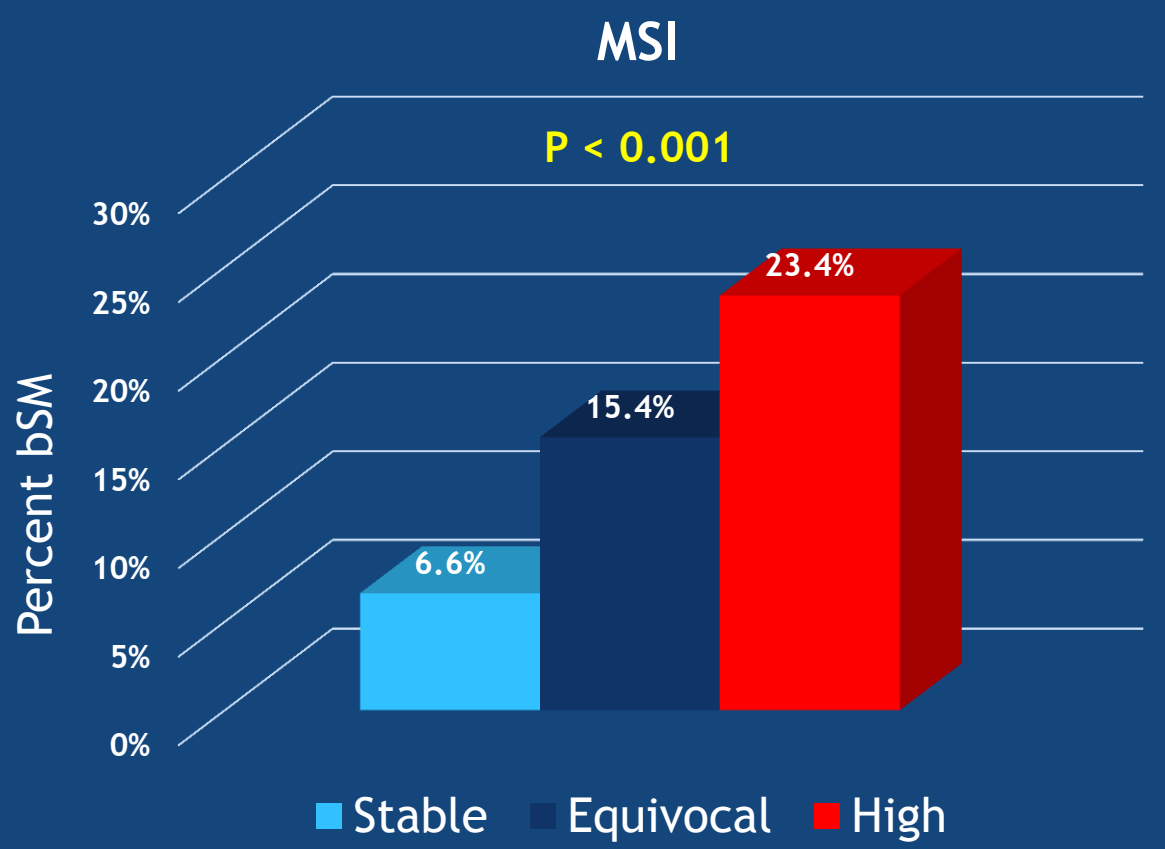


Association of MMR mSM with MSI-H

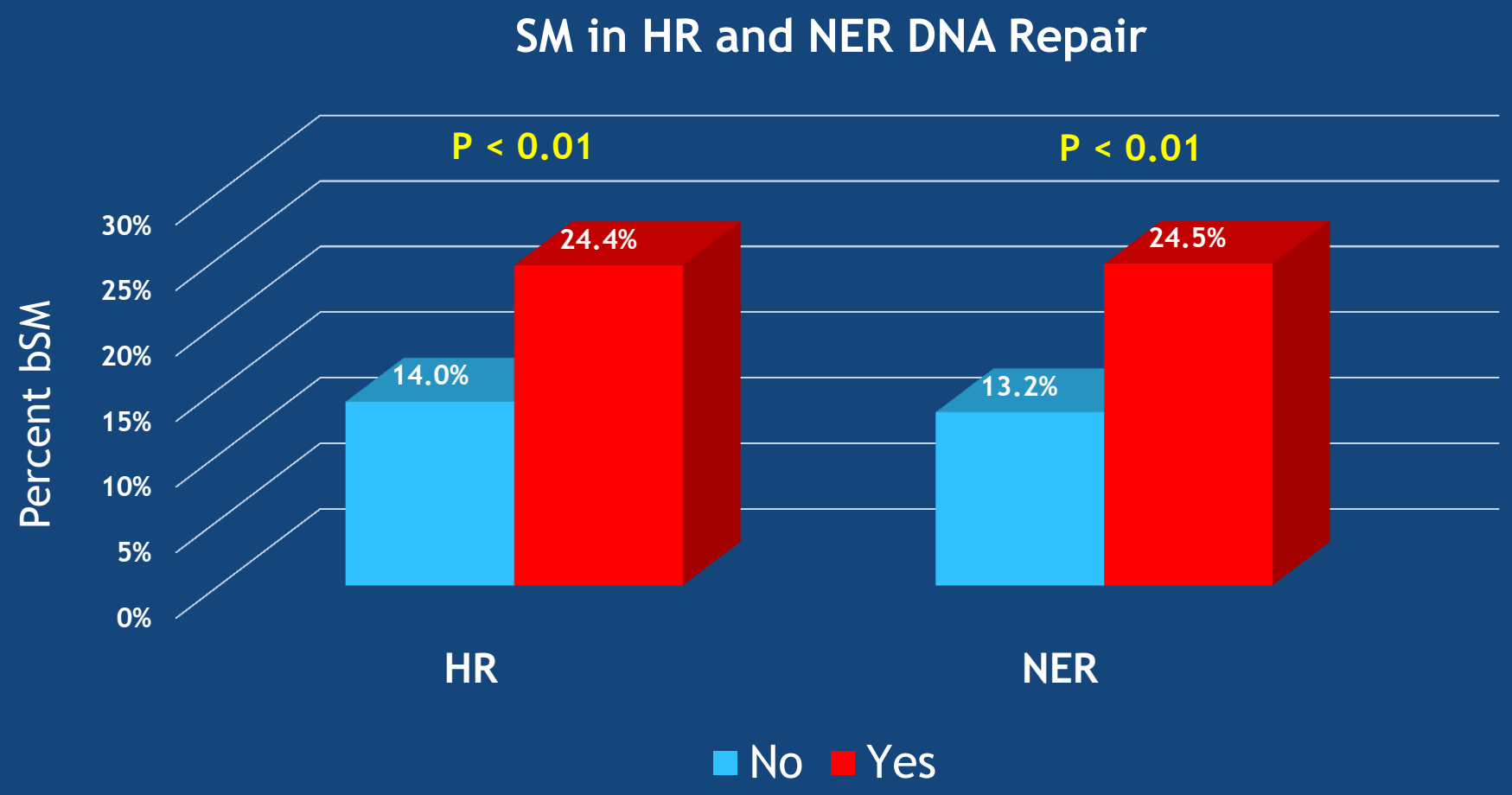


Association of MMR bSM with TMB and MSI





Association of MMR bSM with SM in HR and NER DNA Repair Pathways



Associations between MMR bSM and SM in HR and NER DNA Repair

MMR genes	OR	(95 % CI)	OR	(95 % CI)
		HR		NER
bSM vs. no mutations				
MLH1	4.21	(1.49 – 11.84)**	2.06	(0.77 – 5.53)
MSH2	10.30	(4.13 – 25.65)**	2.24	(0.96 – 5.23)
MSH6	3.82	(1.75 – 8.33)**	2.97	(1.40 – 6.26)**
PMS2	0.55	(0.10 – 3.14)	0.49	(0.11 – 2.24)

Study Limitations

- No paired germline data therefore unknown if the somatic mutations observed are also found in germline, though a number of the mutations identified here have been reported in germline series.

- bSM were assumed to be in trans as the likelihood of two pathogenic mutations on the same MMR gene allele is very low.

- Loss of heterozygosity studies not conducted.

- No individual-level family history data or treatment data.

Summary

❖ MMR mSM are found in a diverse range of tumor histologies.

❖ MMR bSM occur more often in younger patients and primarily in Lynch syndrome spectrum tumors, suggesting:

- Germline MMR mutations precede many bSM and/or
- Some organs are more vulnerable to develop bSM in the setting of mSM

❖ MMR mSM and bSM are associated with high TMB, MSI-H, and mutations in non-MMR DNA repair pathways (i.e. HR and NER DNA repair pathways).

❖ Findings suggest both interactive and cascade effects of DNA repair pathways, which may elucidate tumor biology and new treatment targets.