

# **Esophageal Cancer Cases**

Quiz Questions:

Relationship between proto-oncogene and oncogene?

Examples:

Ras

HER2/neu

MYC

## **Tumor Suppressor Genes**

### **FAP Prophylactic Surgery**

- Total proctocolectomy with ileal pouch
- Total colectomy with ileorectal anastomosis
- Proctocolectomy with end ileostomy

### **Lynch Syndrome Prophylactic Surgery**

- No role for prophylactic colon surgery
- Prophylactic hysterectomy with BSO

## **BRCA 1/2 Prophylactic Surgery**

- Bilateral mastectomy reduces lifetime risk 90%
- Surveillance is a reasonable option
  - Yearly mammogram
  - Yearly breast MRI

## **BRAC 1/2 Prophylactic Surgery**

- Prophylactic BOS age 35-40 or after childbearing
- Reduces risk of ovarian cancer 80%
- Surveillance not as effective
  - Transvaginal ultrasound
  - CA-125 screening

## **MEN 2A/2B or FMTC Prophylactic surgery**

- Timing of thyroidectomy depends upon risk category
- Highest risk: Thyroidectomy within first year of life
- High risk: Thyroidectomy by age 5 or if calcitonin elevated
- Moderate risk: surveillance starting age 5
  - physical exam
  - neck ultrasound
  - serum calcitonin

## **FAP**

Median age of dx 39

- Duodenal and ampullary tumors
- Gastric polyps
- Thyroid tumors
- Desmoid tumors

## **FAP screening**

Colonoscopy age 10-12 EGD for duodenal polyps at age 20-30  
CT 1-3 years after colectomy and q5 yrs in those with family hx of desmoids

## **Lynch**

Amsterdam Criteria

(Bethesda Criteria)

Mean age dx colon cancer 44-61 Predominant right side colon cancer Lifetime penetrance 82%

## **Lynch Other Cancers**

- Endometrial
- Stomach
- Ovarian
- Urinary tract
- Biliary Tract
- Small bowel
- CNS

## **Lynch Screening**

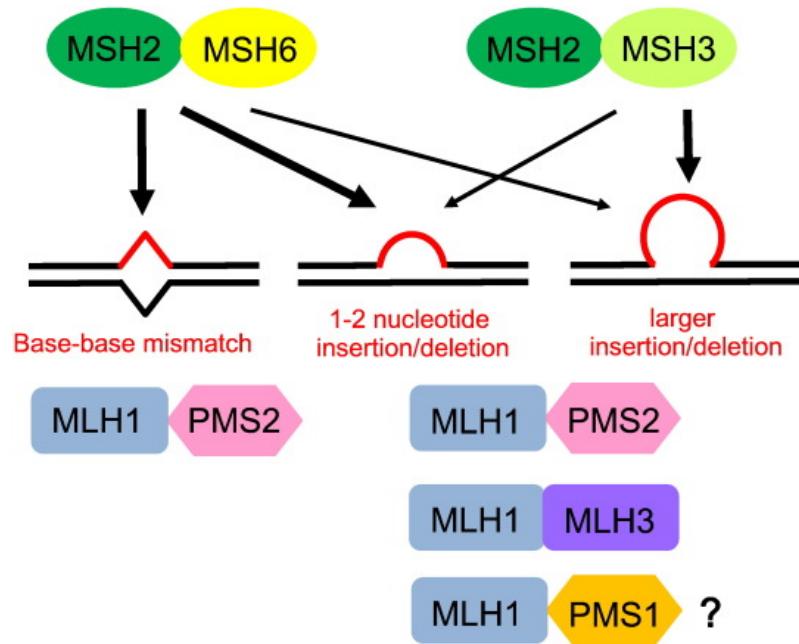
Colonoscopy q1-2 years starting age 20-25

Women with Lynch have 25-60% lifetime risk of endometrial cancer 45-12% lifetime risk of ovarian cancer Male: 1.2% risk of breast cancer (0.1% in general populations)

## MMR and MSI

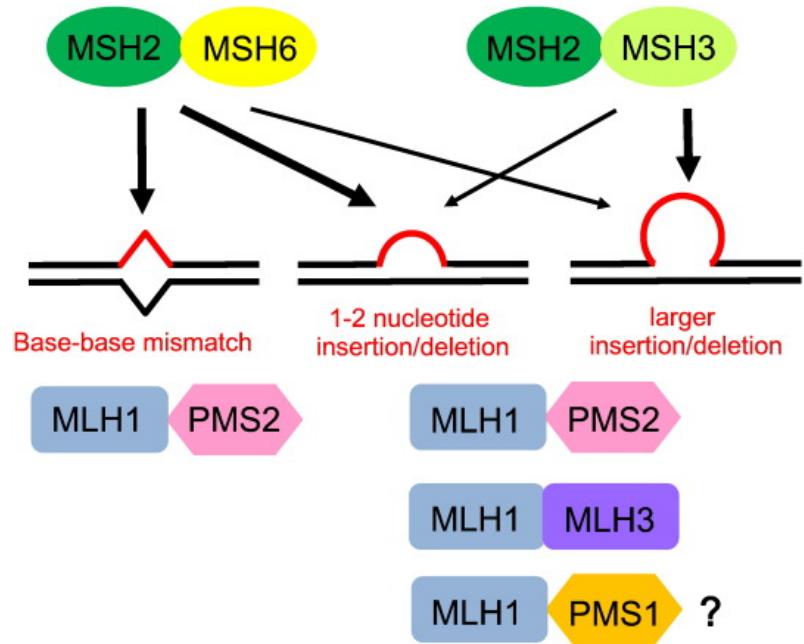
Greater than 90% of LS tumors are MSI-high (MSI-H) and/or lack expression of at least one of the MMR proteins by IHC. Ten percent to 15% of sporadic colon cancers exhibit abnormal IHC and are MSI-H most often due to abnormal methylation of the MLH1 gene promoter, rather than due to LS. Mutant BRAF V600E is found in many sporadic MSI-H CRCs and is rarely found in LS-related CRCs. There are some tumors that will have MLH1 methylation but lack a BRAF PV.

## DNA Mismatch Repair Proteins

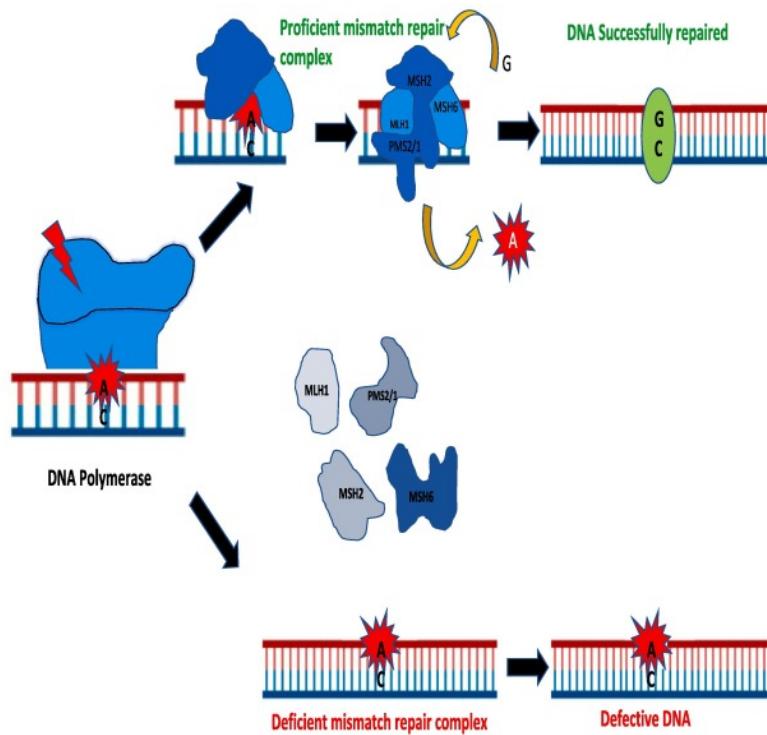


## DNA Mismatch Repair Proteins

MLH1 PMS1 MSH6 MSH2 MSH5



## DNA Mismatch Repair Proteins



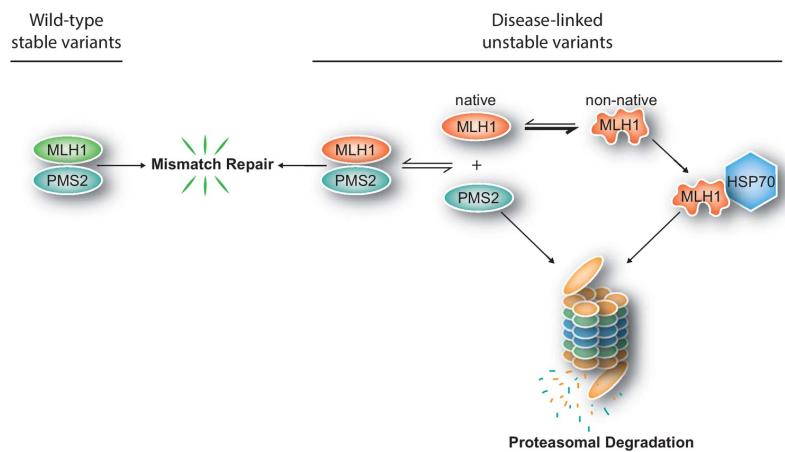
## Mismatch Repair Proteins in Lynch Syndrome

Lynch Syndrome can be caused by loss of expression of:

- MLH1
- PMS1
- MSH6
- MSH2
- MSH5

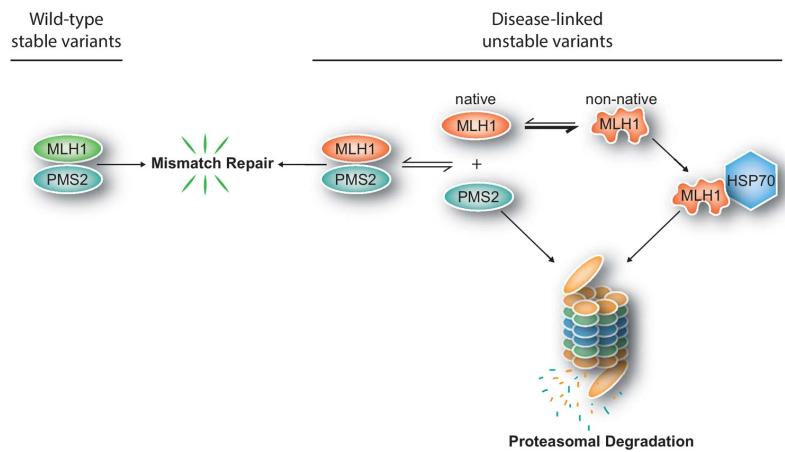
## MLH1 and PMS Dimer in Mismatch Repair

wild-type MLH1 and PMS2 form a stable heterodimer



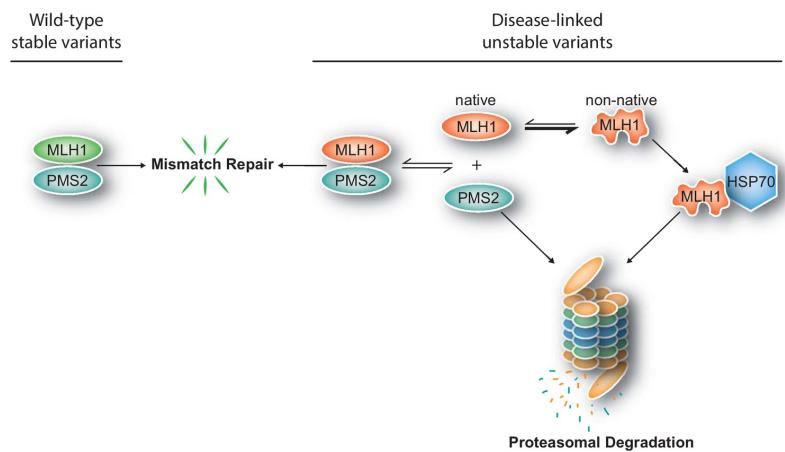
### MLH1 and PMS Dimer in Mismatch Repair

Mutant MLH1 fails to form a stable heterodimer



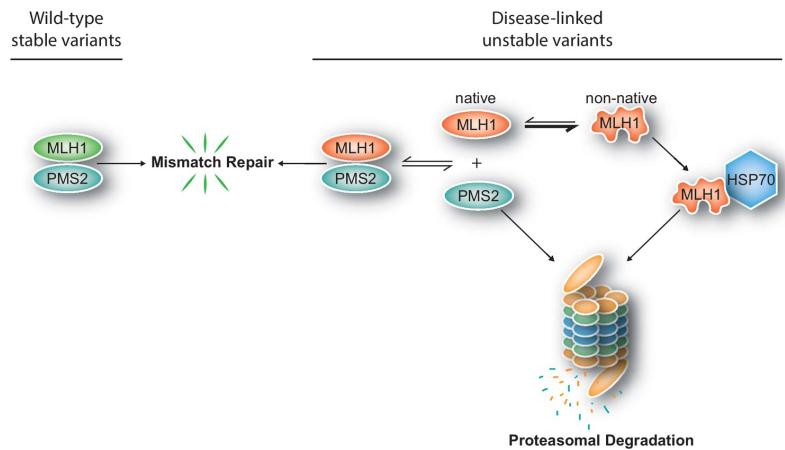
### MLH1 and PMS Dimer in Mismatch Repair

Mutant MLH1 fails to form a stable heterodimer → PMS2 is degraded



## MLH1 and PMS Dimer in Mismatch Repair

If MLH1 is mutated → PMS2 protein is *not* detected



Heterodimer pairings of mismatch repair proteins hold the key to interpreting the results from IHC testing.

MLH1 and PMS2 form a heterodimer. MLH1 forms heterodimers with other mismatch repair proteins as well, but PMS2 only binds with MLH1. As a result, loss of MLH1 function will automatically lead to loss of PMS2 staining because it doesn't have its binding partner. The reverse is not true, however, because MLH1 can still bind with one of its other partners.

MSH2 and MSH6 form another heterodimer. Like MLH1, MSH2 sometimes forms a heterodimer with other mismatch repair proteins. Like PMS2, MSH6 only binds with MSH2. Loss of MSH2 function will therefore automatically lead to loss of MSH6 staining, but not vice versa.

Typically, IHC staining for the mismatch repair proteins is interpreted as follows:

Loss of MLH1 and PMS2 protein staining may indicate a germline MLH1 mutation or somatic MLH1 promoter hypermethylation; additional testing (BRAF V600E mutation analysis or MLH1 hypermethylation analysis) may be useful in distinguishing between these possibilities  
Loss of PMS2 protein staining usually indicates a germline PMS2 mutation  
Loss of MSH2 and MSH6 protein staining usually indicates a germline MSH2 mutation  
Loss of MSH6 protein staining usually indicates a germline MSH6 mutation

Clinicopathological features of BRAF V600E MT CRC patients  
Molecular features of BRAF V600E MT CRC  
1. Age >70 years  
2. Female patients  
3. More CIMP  
4. Proximal right-sided tumours  
5. More MLH-1 methylation  
6. High-grade and poorly differentiated  
7. Mutually exclusive to KRAS mutation  
8. Mucinous>non-mucinous  
9. More peritoneal and lymph node metastases  
10. Less lung metastases  
Table 3.

## **BRAF V600E Mutations in Colorectal Cancer**

1. Age >70 years
2. Female patients
3. Proximal right-sided tumours
4. High-grade and poorly differentiated
5. Mucinous>non-mucinous
6. More peritoneal and lymph node metastases

### **Colon Polyposis: >10 adenomatous polyps**

- Classical FAP
- Attenuated FAP (AFAP)
- MUTYH-associated polyposis (MAP)
- Colonic adenomatous polyposis of unknown etiology (CPUE)

### **Colon Polyposis: >4 hamartomatous polyps**

- Puzet-Jaggers
- Juvenile Polyposis Syndrome
- Cowden Syndrome/PTEN Hamartoma Tumor Syndrome

### **Serrated Colon Polyps**

5 serrated polyps/lesions proximal to the rectum, all being 5 mm in size, with 2 being 10 mm in size OR >20 serrated polyps/lesions of any size distributed throughout the large bowel, with 5 being proximal to the rectum

### **Muir-Torre Syndrome**

Muir-Torre syndrome refers to individuals with LS who have LS-associated skin findings of sebaceous adenomas/carcinomas or keratoacanthomas.

### **BRCA 1/2**

BRCA1: 87% lifetime risk of breast cancer and 40-60% risk of ovarian cancer

BRCA2: 80% lifetime breast cancer and 15-27% ovarian cancer - Elevated risk of prostate, pancreas, melanoma

Male carriers of BRCA2: 8.9% lifetime risk of breast cancer

## **BRCA risk factors:**

- Breast cancer dx before age 40
- Bilateral breast cancer
- Breast and ovarian cancer
- 2 family members with breast cancer < age 50
- Family history of breast and ovarian
- Family history of male breast cancer

## **Attenuated FAP**

~30 polyps 70% penetrance by age 80 - mean age at dx 50-55

## **Li-Fraumeni**

Mutation of TP53 tumor suppressor gene

- Breast cancer 90% by age 50
- Sarcoma
- Leukemia
- Brain tumors
- Andrenocortical carcinoma

## **Breast cancer in Li-Fraumeni**

Mastectomy favored to avoid radiation therapy

Bilateral prophylactic mastectomy recommended

## **p16 = CDKN2A mutation**

- Increased risk of melanoma
  - Familial Atypical Multiple Mole Melanoma (FAMMM)
  - Familiar Atypical Multiple Mole-Pancreatic Carcinoma (FAMMMPC)
- Melanoma penetrance 58-92% by 80
- Pancreatic cancer penetrance 17% by age 75

## **FAMMM**

- Malignant melanoma in one or more first degree or second-degree relatives
- High total body nevus count
- Nevi with certain features on microscopy

Genetic testing not performed as only 50% of FAMMM harbor a mutation in CDKN2A

## **Neurofibromatosis 1**

Mutation in NF1 tumor suppressor gene

- Multiple neurofibromas
- Cafe au lait spots
- Lisch nodules (hamartoma of the iris)

Risk of - NPNST - Pheochromocytoma - Astrocytoma - Leukemia

## **NF1 diagnosis**

Two or more of the following 6 criteria:

- Six or more café-au-lait macules
- Two or more neurofibromas or one plexiform neurofibroma
- Axillary or inguinal freckling
- Optic glioma
- Two or more Lisch nodules
- Characteristic osseous lesions
- A first degree relative with NF1

## **Neurofibromatosis 2**

NF2 gene

- Multiple neurofibromas
- Cafe au lait spots
- Bilateral vestibular schwannomas

- CNS tumors

Most affected develop bilateral schwannomas by age 30 with average age of death 26

Annual surveillance MRI starting age 10-12 and hearing evaluationm

## **PTEN**

Cowden Syndrome Mutation in *PTEN* tumor suppressor gene

- Mucocutaneous facial lesions
- Macrocephaly
- Bilateral breast cancer
- Thyroid and endometrial tumors
- Hamartomatous polyposis of the GI tract

## **MEN1**

- Mutation of MENIN tumor suppressor
- Parathyroid
- Pituitary
- Pancreatic islet cells

Hyperparathyroidism usually first presentaiotn Most common pancreatic tumor is non-functional

Dx by 2/3 of following:

- Parathyroid adenoma/hyperplasia
- Pancretic islet cell tumors
- Pituitary tumors

## **MEN1 screening**

Surveillance with serum prolactin, IGF-1, fastin glucose and insuslin starting age 5 Calcium,, chormogranin A, pancrea polypeptide glucaon AP age 8 Serum gastrin starting age 20 Brain MRI starting age 5 Abdomeal CT/MRI stagting age20

## **MEN1 surgical treatment**

Parathyroidectomy 3.5 gland or 4 glands with autotransplantation

Pancreatic tumor resection if >2cm

Pituitary tumors resected via transsphenoidal

## **MEN2 Family of Syndromes**

- RET proto-oncogene
- Medullary thyroid cancer in almost 100%
- MEN2A
  - pheochromocytoma in 50%
  - Parathyroid hyperplasia in 20-30%

-MEN2B - pheochromocytoma in 50% - Megacolon - Marfanoid habitus - Ganglioneromas - Mucosal neuromas

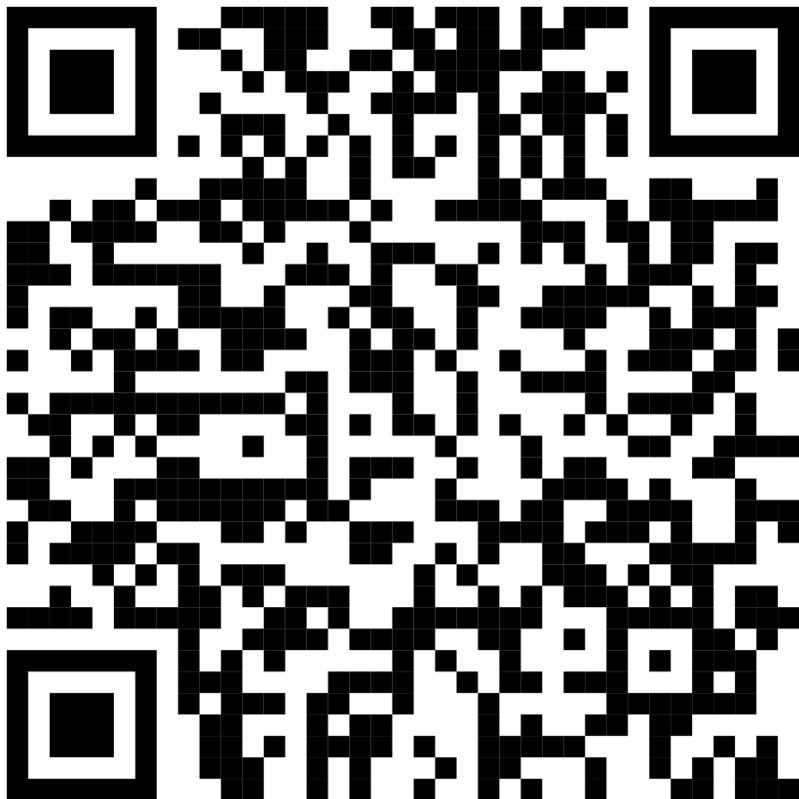
## **MEN 2 Prophylactic surgery**

Prophylactic total thyroidectomy

Testing for pheochromocytoma prior with adrenalectomy prior

Monitor calcitonin and CEA after thyroidectomy

## **Orientation Handbook**



## **References**