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Pearl Title: Hereditary endometrial carcinoma (with a focus on Lynch syndrome)

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Overview

- Definition of Lynch syndrome
- Recommended screening guidelines
- Screening tools: IHC, MSI testing and more
- Diagnostic tools: gene sequencing and dosage
- Underlying molecular mechanism
- Role of genetic counseling
- Summary

Lynch Syndrome

- Another name for Hereditary Non-Polyposis Colorectal Carcinoma (HNPCC)
- Associated with carcinoma of different organs most importantly colorectal and endometrial and less commonly gastric, ovarian, small bowel and pancreatic
- Younger age at time of cancer diagnosis, multiple cancer types and multiple family member involvement

Other Forms of Hereditary Endometrial Carcinoma

- *PTEN* germline mutation – Cowden syndrome
  - Second most common cause of hereditary endometrial carcinoma
  - Associated with increased risk for thyroid, breast and endometrial carcinoma
  - Patients have a 28% life time increased risk for developing endometrial carcinoma
- Other causes: *EPCAM* gene deletions (causing MSH2 inactivation), *POLE* and *POLD1* germline mutations

Screening guidelines

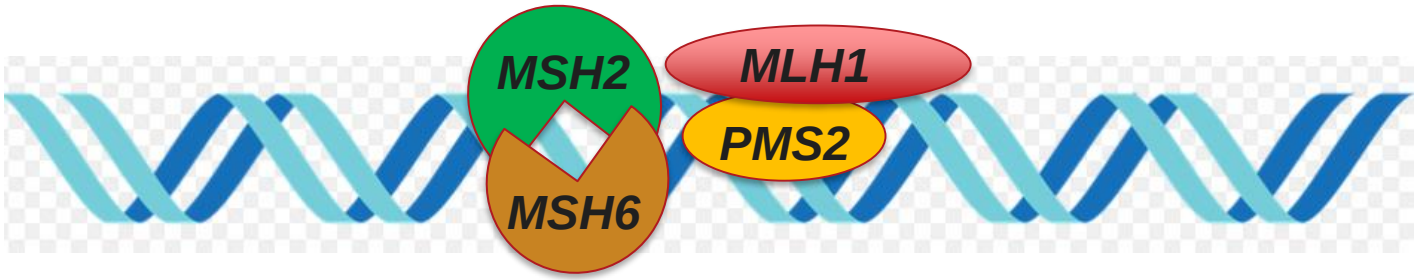
- Revised Bethesda criteria, 2004:
  - At least three relatives with any Lynch associated cancer (colorectal, endometrium, small bowel, ovary, stomach, pancreas) with at least one relationship being first degree relative
  - At least two successive generations should be affected
  - At least one family member with cancer diagnosis before age of 50
  - Familial Adenomatous Polyposis (FAP) should be excluded
- Universal screening: recent guidelines by NCCN and ACS: ANY patient or at least those younger than 60 years old, with a new diagnosis of endometrial and/or colorectal carcinoma should be screened for Lynch syndrome

Genes and pattern of inheritance

- Four major genes located on chromosomes 3, 7 and 2
- Genes: *MLH1*, *PMS2*, *MSH2* and *MSH6*
- Autosomal dominant, variable penetrance
- Lynch syndrome patients have a 40-60% lifetime chance for endometrial and similar risk for developing colorectal carcinoma
- Lynch syndrome patients have higher chance of cancer with *MLH1* and *MSH2* mutations and the lowest chance with *PMS2* mutations

Function of MMR genes

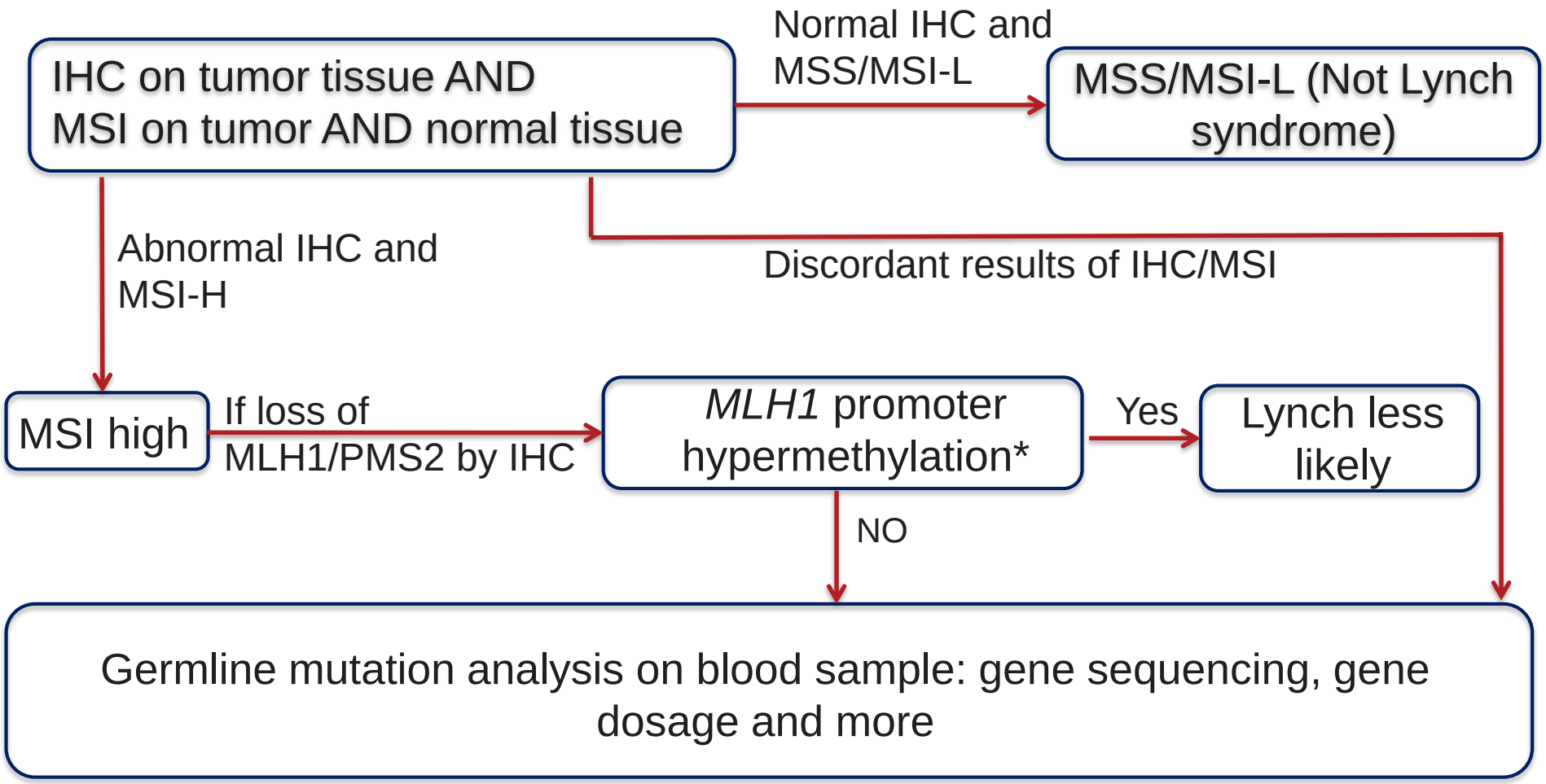
- DNA replication at the repetitive regions can be associated with slip and bubbles/loops formations
- These mistakes (bubbles, loops) are corrected by MMR enzymes
- *MLH1/PMS2* and *MSH2/MSH6* are two protein dimers involved in mismatch repair during DNA synthesis



Screening testing for Lynch syndrome

- IHC for MMR gene defects: Look at protein expression of *MLH1*, *PMS2*, *MSH2* and *MSH6* by using specific antibodies directed against each
- MSI (using short tandem repeat markers): Often using 5 molecular markers (combination of mono- and di-nucleotide repeat markers)
- *MLH1* hypermethylation testing: rule out somatic alteration resulting in *MLH1* silencing
- Positive screening test → do germline genetic testing, using sequencing and gene dosage

Algorithmic testing in Lynch syndrome

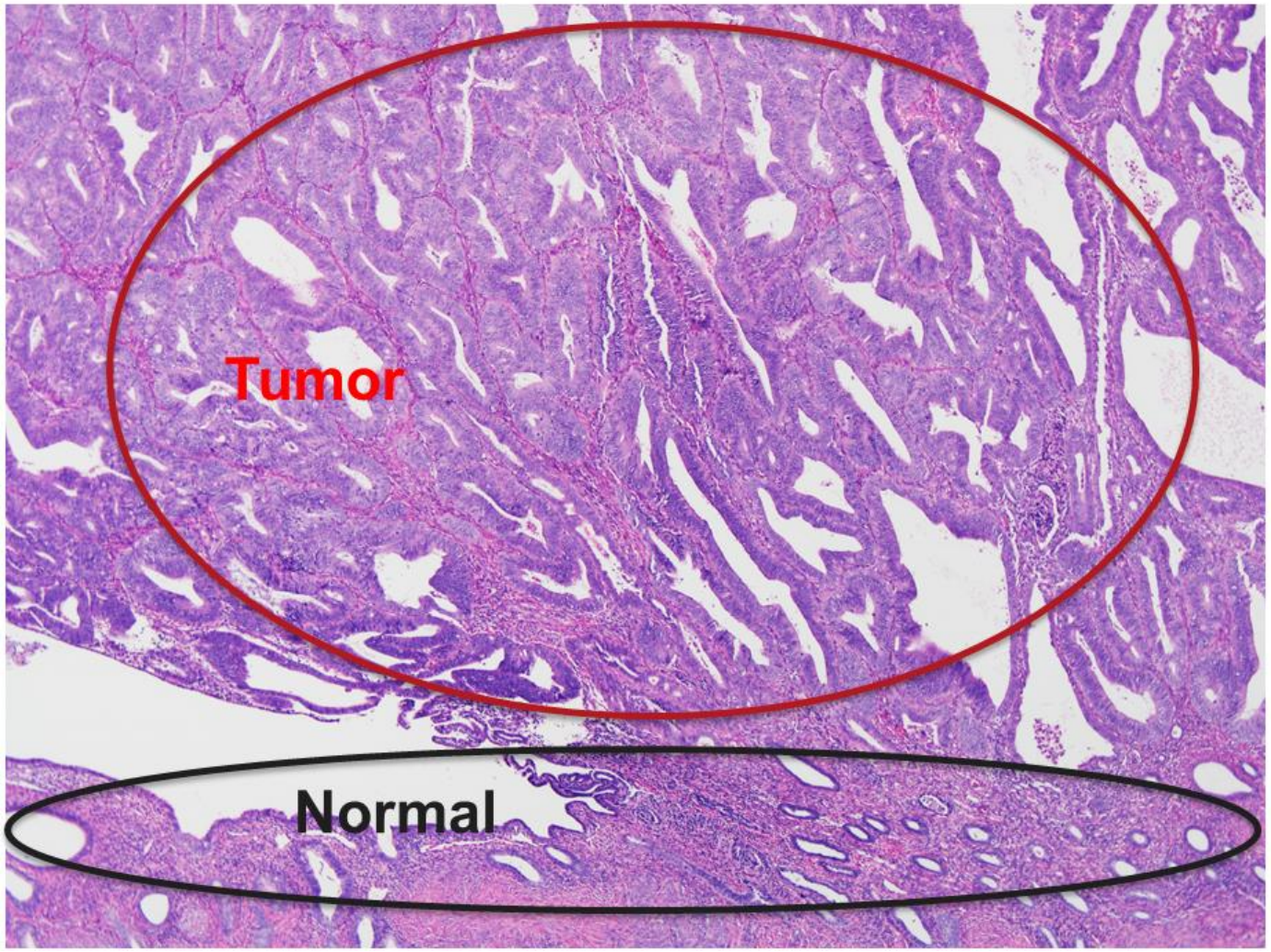


* and *BRAF* V600E mutation in colorectal carcinoma

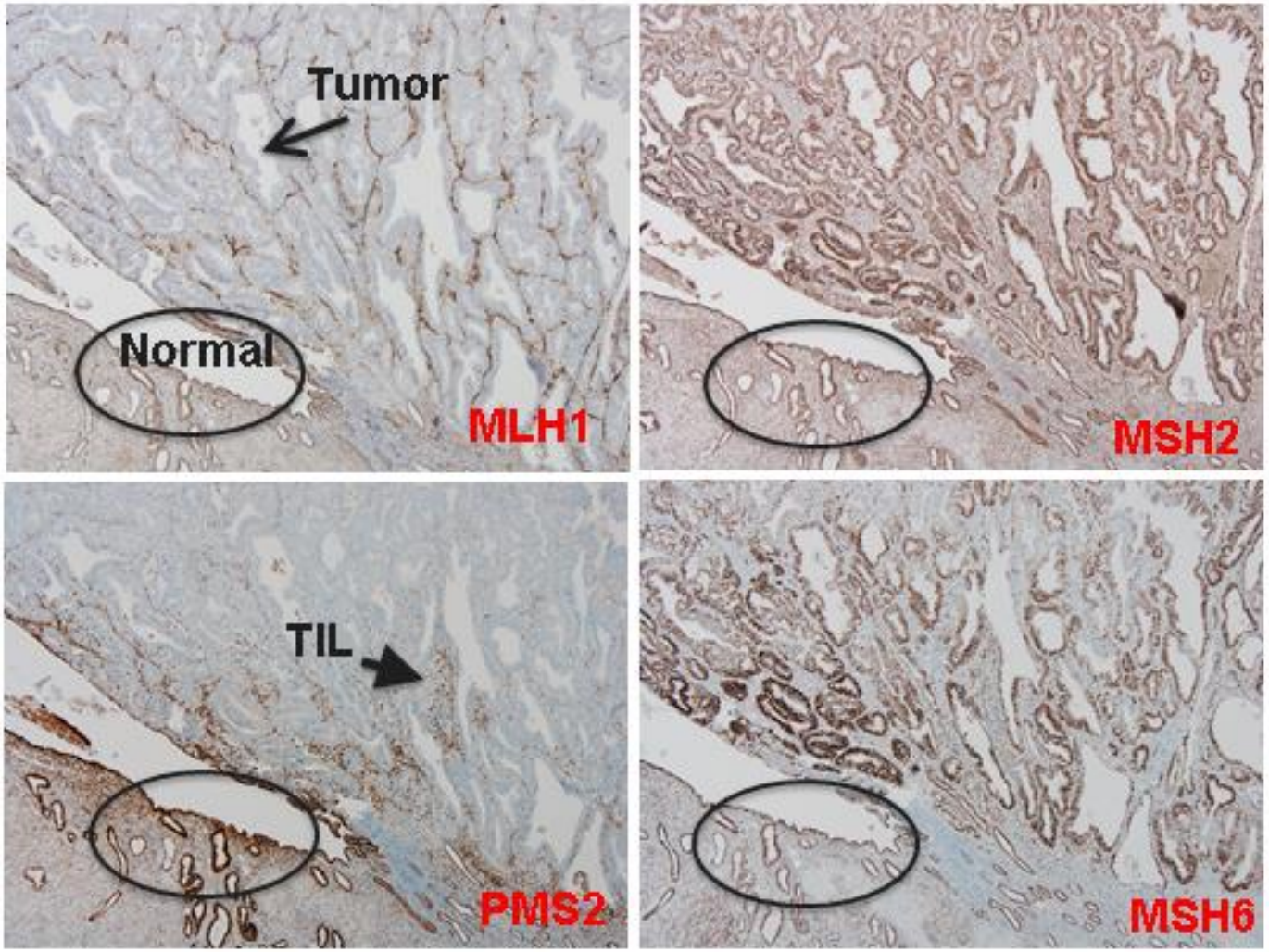
MSI testing

- Microsatellites are short tandem repeats of DNA scattered through the entire human genome, 1-3 or more nucleotides in size
- Abnormal or non-functioning MMR proteins (due to germline or somatic mutations) will cause shifts in microsatellite size in the repetitive regions of genome
- DNA extraction from normal and tumor area -- > capillary EP of PCR products
- It is recommended to use 5 markers (mono- and di-N):
  - Instability in >=2/5 (>30% of markers): MSI-H
  - Instability in 1/5 markers (1-29%): MSI-L
  - Instability in 0/5 markers (<1%): MSS

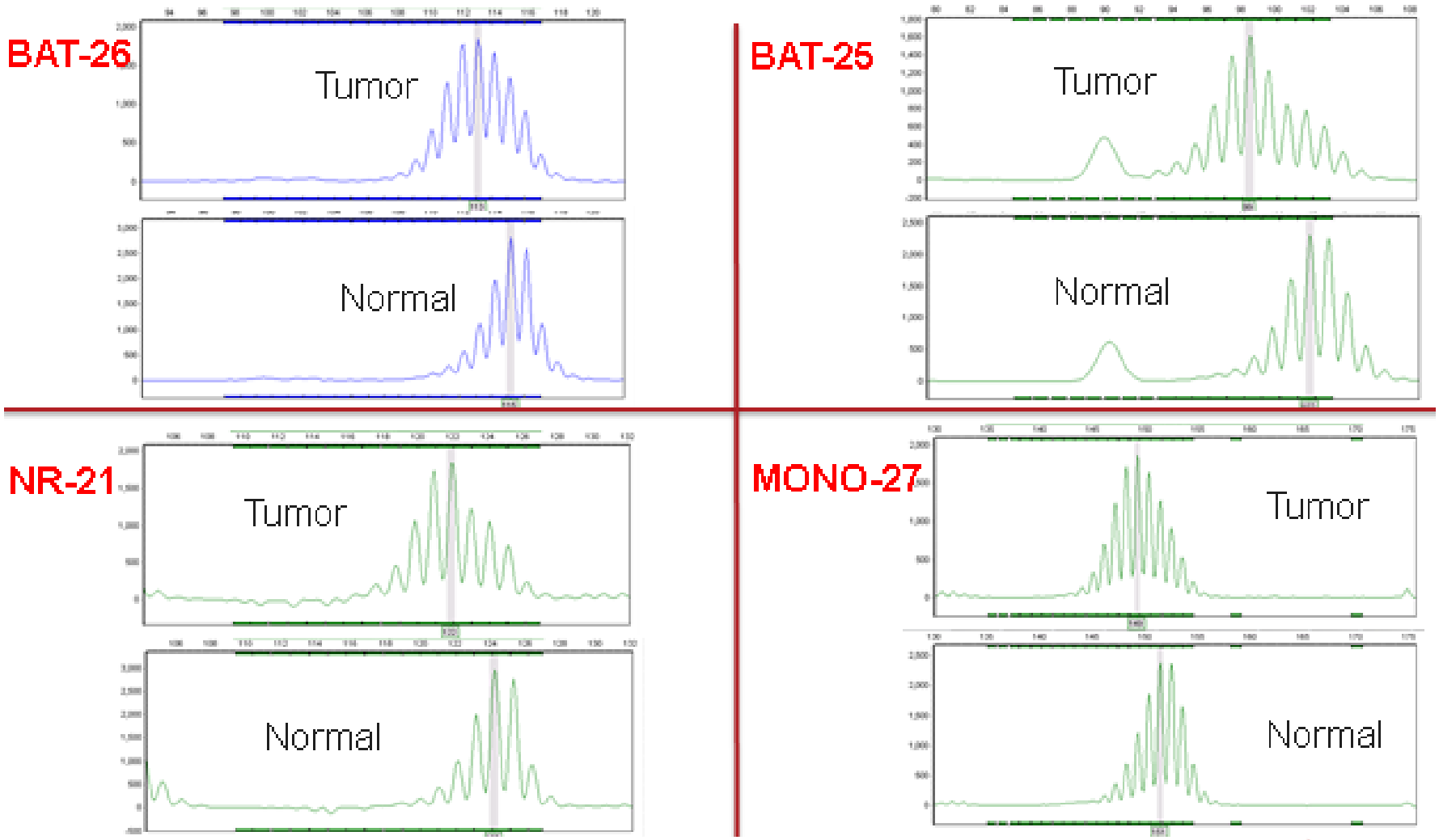
Example case- H&E



Example case- MMR IHC



Example Case- MSI



Histomorphology and prognosis

- Colorectal carcinoma with MSI-H: mucinous or signet ring cell morphology, increased intratumoral lymphocyte, poorly differentiated (medullary like) morphology and a Crohn's like response at the edge of the tumor

- Endometrial carcinoma with MSI-H: Less established, but associated with more peritumoral and intratumoral lymphocytes and tumor heterogeneity including different tumor histology (endometrioid and serous)

- Colorectal MSI-H carcinomas have better prognosis and data on MSI-H endometrial carcinomas is controversial

Genetic Counseling

- Patients with Lynch syndrome have higher risk for developing multiple primary malignancies and will benefit from closer monitoring
- Genetic counseling should be offered to both patients and their family members, usually after finding of abnormal IHC and/or MSI result
- Early detection of individual at risk for developing cancer is beneficial

Summary

- Cancer predisposition syndrome with increased risk of colorectal, endometrial, ovarian, small bowel, sebaceous, gastric and pancreatobiliary carcinoma
- Most patients with Lynch syndrome have a germline mutation in one of the 4 MMR genes, most commonly in the *MLH1* or *MSH2*
- *MLH1* hypermethylation (predominantly a somatic alteration) should be ruled out
- Diagnostic and screening guidelines help identify patients and their family members who are at risk for developing Lynch syndrome related carcinomas

Figure/Table Title

- Figure1. Function of MMR genes, personal collection
- Figure 2. Algorithmic testing in Lynch syndrome, personal collection
- Figure2. H&E photomicrograph of an example, personal collection
- Figure3. Mismatch Repair protein expression by IHC, personal collection
- Figure4. MSI testing, personal collection

References

- W Kohlmann, SB Gruber - 2014 - ncbi.nlm.nih.govOrganisation mondiale de la santé, and Centre international de recherche sur le cancer. WHO classification of tumours of female reproductive organs. IARC press, 2014.
- J.M. Lancaster, C.B. Powell, L.M. Chen, D.L. RichardsonSociety of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol, 136 (2015), pp. 3-7
- Stoffel, Elena M., et al. "Hereditary colorectal cancer syndromes: American society of clinical oncology clinical practice guideline endorsement of the familial risk–colorectal cancer: European society for medical oncology clinical practice guidelines." Journal of clinical oncology 33.2 (2014): 209-217.
- Umar, Asad, et al. "Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability." Journal of the National Cancer Institute 96.4 (2004): 261-268.
- American College of Obstetricians and Gynecologists Practice Bulletin: Lynch Syndrome; available from: URL: https://www.sgo.org/wp-content/uploads/2012/09/2014-ACOG-bulletin.pdf
- https://www.asco.org/practice-guidelines/cancer-care-initiatives/genetics-toolkit/management-individuals-increased
- https://www.sgo.org/clinical-practice/guidelines/screening-for-lynch-syndrome-in-endometrial-cancer/
- Lynch syndrome. https://www.omim.org/entry/120435

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