ACS Cancer Conference 2025

March 12–14 | Phoenix, AZ

Genetics and Genomics of Cancer

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ACS Cancer Programs

American College of Surgeons

Colon cancer Focus

Genetics of Colon Cancer- Sporadic Cancer

- Genetic mutations occur within the tissue over time
  - nucleotide changes in the coding region of genes causing the product of these genes to be dysfunctional (as in the case of tumor suppressors),
  - increased function of oncogenes,
  - copy number changes where chromosomes are amplified or deleted, or
  - epigenetic alterations causing altered transcription of genes through promoter methylation.

- In CRC, the recurrently altered pathways are in WNT, MAPK, PI3K, TGF-β, and p53 pathways.
- Genetic alterations are only clinically relevant if they are shown to be biomarkers of disease or if they can be targeted with treatment.

Colon Cancer Genetics

- Mutations leading to CRC
  - APC – most common gene altered in colon cancer. Loss results in transcription upregulating multiple pathways.
  - TP53- tumor suppressor gene. Associated with advanced disease. Loss results in increased proliferation, decreased DNA repair, and decreased apoptosis
- Clinically relevant mutations
  - RAS (including KRAS and NRAS)- non-responsive to anti-EGFR agents
  - BRAF: important as a dictator of worse prognosis in stage 4 patients
  - epithelial-to mesenchymal transition (EMT) pathway
- Hypermutated tumors –usually with 1000s of mutations. Typically harbor genetic or epigenetic alterations in the mismatch repair genes causing rapid accumulation of mutations.
  - More resistant to typical chemotherapy
  - Better prognosis
  - Immunotherapy responsive

Additional Genetic Pathways

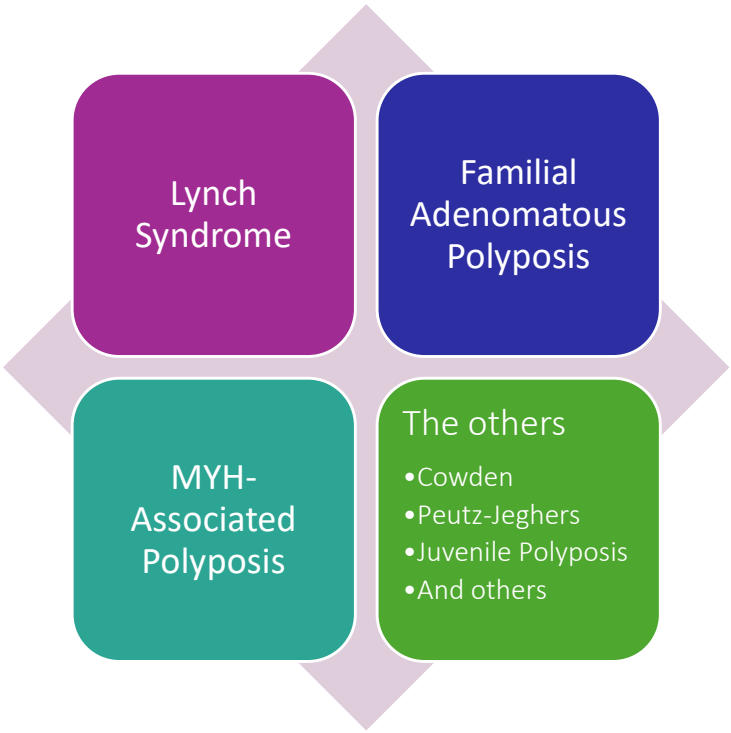
- Chromosomal Instability (CIN)
  - include loss of 8p, 17p, and 18q and gains in chromosomes 8q, 13, and 20q.

- Epigenic Alterations
  - CpG island refers to a specific molecular subtype characterized by widespread hypermethylation (excessive methylation) of CpG islands, which are DNA regions rich in cytosine-phosphate-guanine (CpG) sequences, leading to the silencing of tumor suppressor genes.
  - This is the mechanism for many sporadic microsatellite unstable (MSI-high, or MSI-H) tumors whereby the promoter of the mismatch repair MLH1 gene is silenced by hypermethylation. These tumors then lack functional MLH1 protein and then accumulate genetic mutations quickly because they lack this form of DNA repair.
  - This CpG island methylator phenotype (CIMP) is found in sessile serrated adenomas and the cancers that arise from them. These tumors commonly harbor BRAF mutations.

Consensus Molecular Subtypes (CMS)

- CMS1:
  - hypermutated, MSI-high tumors with a high immune infiltrate
- CMS2:
  - tumors have alterations upregulation of WNT and MYC targets along with increased expression of EGFR and HER2
- CMS3:
  - classified by metabolic dysregulation and characterized by KRAS 22 Sporadic and Inherited Colorectal Cancer: How Epidemiology and Molecular Biology Guide Screening and Treatment 400 mutations
- CMS4:
  - activated EMT with increased TGFβ, extracellular matrix, and integrins.

Genetic Syndromes associated with Colon Cancer



- Lynch Syndrome
  - Most commonly inherited (3%)
  - Autosomal Dominant
  - Germline testing for the mutation
  - Defect in mismatch repair genes
  - Consider associated BRAF mutation

- FAP
  - Approximately 1%
  - Autosomal Dominant with 100% penetrance
  - monoallelic mutation of the APC gene, a tumor suppressor located on chromosome 5q21.
  - Adenoma formation occurs when the second gene copy is rendered nonfunctional through an acquired mutation or loss.
  - Attenuated varities have partially affected APC gene

Lynch subtypes

	CRC	Endometrial	Ovarian
PMS2	8.7-20%	13-26%	1.3-3%
MLH1	46-61%	34-54%	4-20%
MSH6	10-44%	16-49%	<1-13%
MSH2/EPCAM	33-52%	21-57%	8-38%
Population	4.1%	3.1%	1.1%

NCCN, v 3.2024

Germline Genetic testing available

- **Invitae Hereditary Cancer Panel**: A test that screens for inherited mutations in genes associated with an increased risk of colorectal cancer, such as *APC*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* (for Lynch syndrome).
- **Color Genomics**: A hereditary cancer test that includes genes related to Lynch syndrome and other inherited cancer syndromes.
- **Myriad Genetics MyRisk™ Hereditary Cancer Panel**: A test that analyzes genes related to various hereditary cancer syndromes, including Lynch syndrome and familial adenomatous polyposis (FAP).
- **Ambry Genetics CancerNext™**: A test that includes both tumor testing and germline genetic testing for inherited cancer risks.

Additional Available Commercial Testing

- **MSI testing**
  - **Promega MSI Analysis System**
  - **MSI Testing by Thermo Fisher Scientific**
- **KRAS, NRAS, BRAF**
  - **Thermo Fisher Scientific Oncomine Colon Cancer Kit**
  - **Illumina TruSight Oncology 500**
  - **FoundationOne CDx by Foundation Medicine**
  - **OncoGuide™ by Thermo Fisher**
- **Next Generation Sequencing**
  - **FoundationOne CDx (by Foundation Medicine)**: This comprehensive test evaluates 324 cancer-related genes and provides information about genetic alterations in the tumor.
  - **Guardant360 (by Guardant Health)**: A liquid biopsy-based test that analyzes cfDNA from a blood sample, providing comprehensive genomic profiling of CRC.
  - **Oncomine Comprehensive Assay (by Thermo Fisher Scientific)**: An NGS test for identifying genetic mutations and alterations in over 50 cancer-related genes.
  - **Caris Molecular Intelligence**: An NGS-based test that evaluates tumor DNA, RNA, and protein markers to guide treatment decisions.

Management of Colorectal Cancer

- Surgery for Stage I-III as upfront treatment
- Mainstay for adjuvant continues to be fluoropyrimidine-based chemotherapy
- Addition of irinotecan and oxaliplatin and targeted therapies have improved survival
- Anti-EGFR (cetuximab and panitumumab): Used in RAS^{WT} metastatic CRC with a negative selection for KRAS mutations
- Newer targets of HER2 amplification and PIk3CA mutation

ORIGINAL ARTICLE

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

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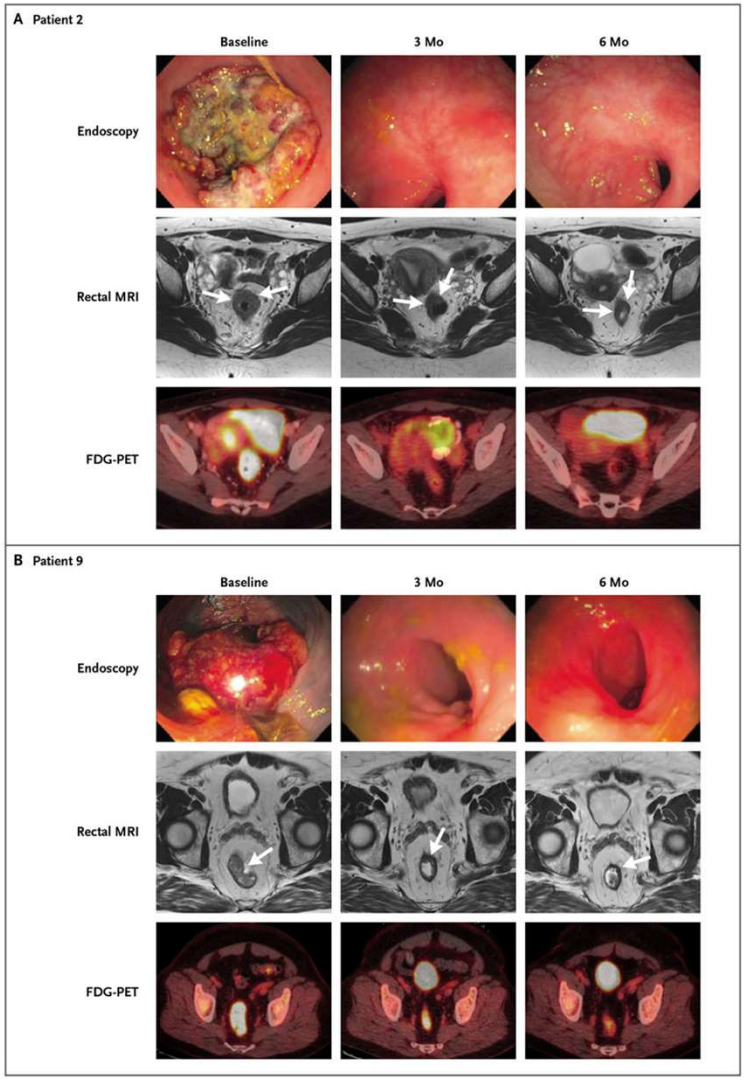
Published June 5, 2022 | N Engl J Med 2022;386:2363-2376 | DOI: 10.1056/NEJMoa2201445 | VOL. 386 NO. 25



Organ Preservation

- Role of Watch and wait in organ preservation with TNT in addition to the role of immunologic therapy.
- Use beyond Rectal Cancer

Management Considerations for MSI-H tumors

- NICHE, NICHE 2 and VOLTAGE A studies
  - Anti PD1 and Anto CTLA-4

- Microsatellite unstable:
  - 15% Stage 3
  - 5% Stage 4

- Consider immunotherapy for metastatic, unresectable, or borderline resectable MSI-high tumors

Circulating Tumor DNA

- CT DNA in
  - Circulate Japan trial, US- BeSpoke
  - Trial large registry trials. Patients did not benefit from adjuvant therapy who had low CT DNA post-op.
  - Circulate North America Trial is in progress- initial data is showing that this may decrease role of adjuvant therapy by allowing us to focus on the patients that will benefit
- Prognostic and better than pathologic staging when done post-op

Genetic Counsellors

Early referral for patients

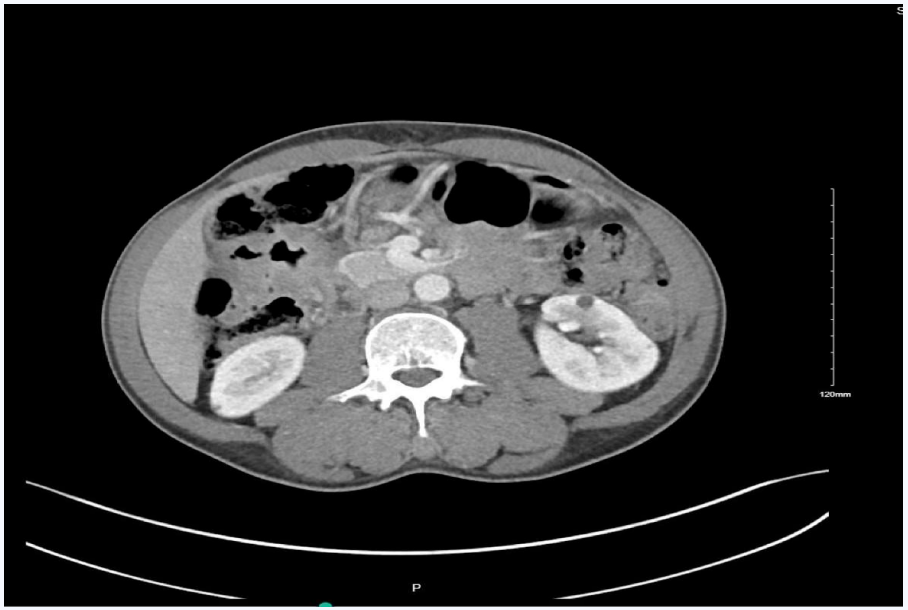
Phenotype (based on cumulative lifetime adenomas)	**Management/Surveillance**
Personal history of ≥100 adenomas	Manage as FAP (FAP-1)
Personal history of 20–<100 adenomas: Adenoma burden that cannot be managed endoscopically	• Surgical evaluation and counseling if appropriate • Baseline upper endoscopy (including complete visualization of the ampulla of Vater[d]) at time of next colonoscopy surveillance by age 20–25 y as on page FAP-B and repeat following duodenal surveillance guidelines on page FAP-C.
Personal history of 20–<100 adenomas: Adenoma burden manageable by colonoscopy and polypectomy	• High-quality colonoscopy and polypectomy every 1–2 y ▸ Repeat at short interval based on residual polyp burden[c] • Baseline upper endoscopy (including complete visualization of the ampulla of Vater[d]) at time of next colonoscopy surveillance by age 20–25 y as on page FAP-B and repeat following duodenal surveillance guidelines on page FAP-C. • Surgical evaluation may be considered if polyps are not manageable or based on patient preference.
Personal history of 10–19 adenomas	• Manage based on clinical judgment. Frequency of surveillance may be modified based on factors such as age at which patient met cumulative adenoma threshold or total number of adenomas at most recent colonoscopy, with more frequent surveillance favored for younger age at meeting threshold or higher adenoma burden at last colonoscopy. See NCCN Guidelines for Colorectal Cancer Screening. • Consider baseline upper endoscopy (including complete visualization of the ampulla of Vater[d]) at time of next colonoscopy surveillance by age 20–25 y as on page FAP-B and repeat following duodenal surveillance guidelines on page FAP-C.

Thank you!

- Questions?

Case

- 71 yo M with a large locally invasive hepatic flexure mass. Pre-operative pathology invasive adenocarcinoma, moderately differentiated. Tumor potentially invading the duodenum
- Guardant and Caris testing, MSI-high
- Treated with neoadjuvant chemo/immunotherapy (FOLFOX-Nivolumab) for 5 months with a great response and significant shrinkage of the primary tumor.



Case

- **Colon with focal necrotizing granulomatous inflammation extending into pericolonic fat, compatible with post-therapy tumor bed, measuring 0.9 cm in greatest dimension.**
- **- No residual tumor seen (complete response, score 0).**
- **- Tumor bed is <1 mm from the radial margin and distant (>10 cm) from the proximal and distal margins.**
- **- Ileocecal valve, appendix and ileum are uninvolved and unremarkable.**
- **- Tissue at distal and proximal resection margins appears viable.**
- **- Eighteen pericolonic lymph nodes, negative for carcinoma (0/18).**
- **- Pathologic stage (AJCC 8th Edition): ypT0N0; see Synoptic data.**