CURRENT GENETICS OF HEREDITARY COLORECTAL CANCER SYNDROMES

South Florida GI Cancer Symposium 2025

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Outline

- Inherited Colorectal Cancer Syndromes
  - Associated Cancer Risks and Screening Strategies
- Novel Approaches to CRC Prevention in High-Risk Individuals
- Future Directions for the Early Detection of CRC in High-Risk Individuals

Inherited Colorectal Cancer Syndromes

- Lynch Syndrome
- Polyposis Syndromes
  - Familial Adenomatous Polyposis (FAP)
  - *MYH*-Associated Polyposis (MAP)
  - Additional rare adenomatous polyposis syndromes
  - Hamartomatous Polyposis

Lynch Syndrome

- **Most common inherited GI cancer syndrome**

  Canonical cancers: Colorectal (CRC) and Endometrial (EC)

- **Common with prevalence 1/300**

  Comparable to Hereditary Breast and Ovarian Cancer Syndrome, BRCA

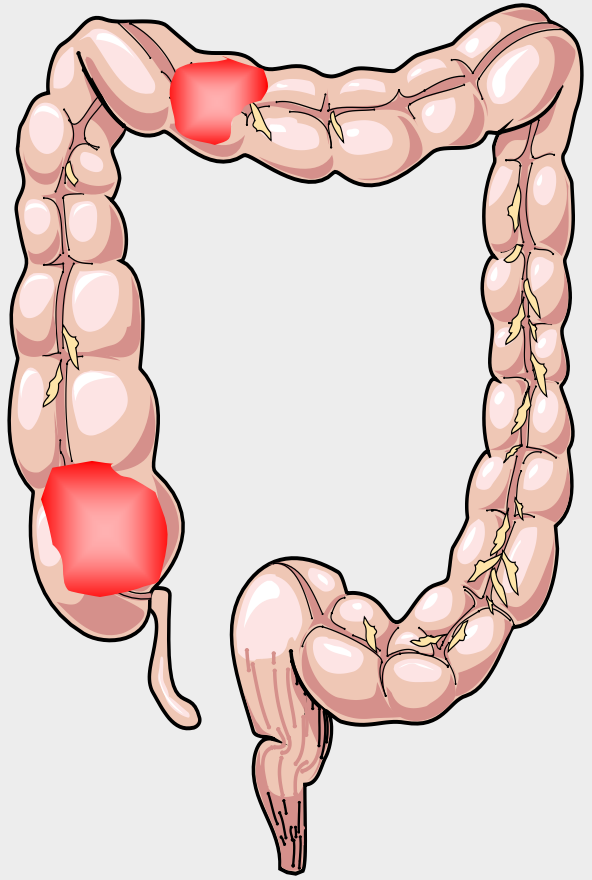
- **MMR deficiency hallmark feature of Lynch syndrome**

  MSI-high phenotype; Loss of MMR protein expression on IHC

  Universal screening of all CRC and EC tumors for MMR deficiency

Lynch Syndrome Clinical Features

- Striking family history affecting multiple generations
- Early (but variable) age at CRC diagnosis
- Multiple primary cancers
- Extracolonic cancers:
  - Endometrium
  - Ovary
  - Urinary tract
  - Gastric
  - Small bowel
  - Pancreas
  - Sebaceous carcinomas of skin



Lynch Syndrome: Genotype Variation in Cancer Prevalence and Risk

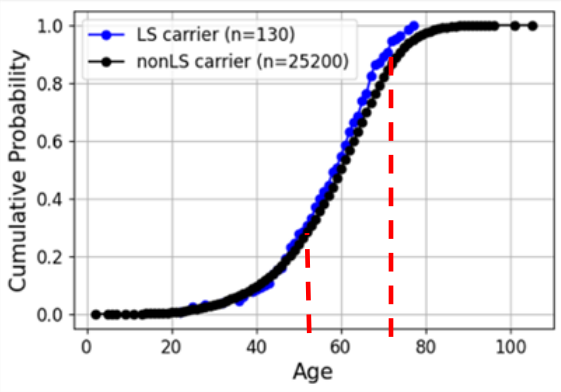
The *All of Us* Research Initiative

- Population-based US cohort study of 1 Million participants

Results

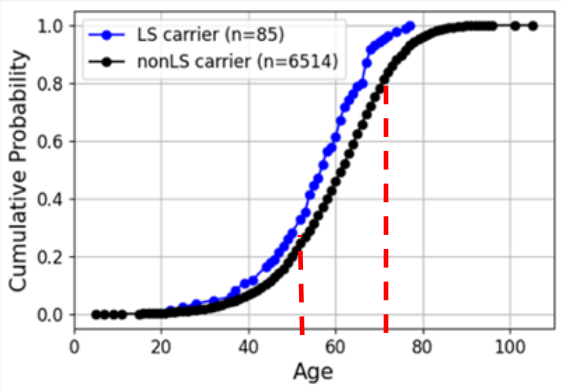
- Prevalence of 1 in 354 individuals; *PMS2* and *MSH6* >> *MLH1* and *MSH2*
- Stronger Phenotype: *MLH1* and *MSH2* >> *PMS2* and *MSH6*

All cancers



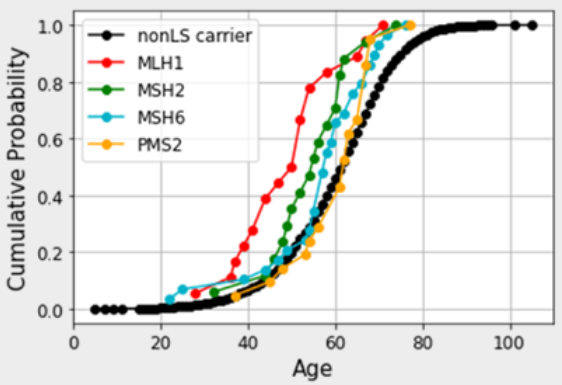
25% vs 22% **87%** vs 79%

LS-associated cancers



26% vs 18% **93%** vs 75%

LS-associated cancers



	Age 50	Age 70
nonLS	18%	75%
MLH1	44%	94%
MSH2	29%	94%
MSH6	21%	90%
PMS2	14%	95%

Park J, et al….Kastrinos F. *Nature Comm,* 2025

Genotype-Specific CRC Screening in Lynch syndrome

- CRC risks in Lynch syndrome vary by Genotype

	Estimated Average Age of Presentation	Cumulative Risk of CRC through 80 years	Colonoscopy screening (initiation age, surveillance interval
MLH1	44 years	46-61%	20-25 years*; repeat every 1-2 years
MSH2	44 years	33-52%	20-25 years*; repeat every 1-2 years
MSH6	42-69 years	10-44%	30-35 years*; repeat every 1-3 years
PMS2	61-66 years	8.7-20%	30-35 years*; repeat every 1-3 years

*Or 2-5 years prior to the youngest diagnosis of CRC in family

NCCN, 2024
Kastrinos, et al. Gastroenterology 2023

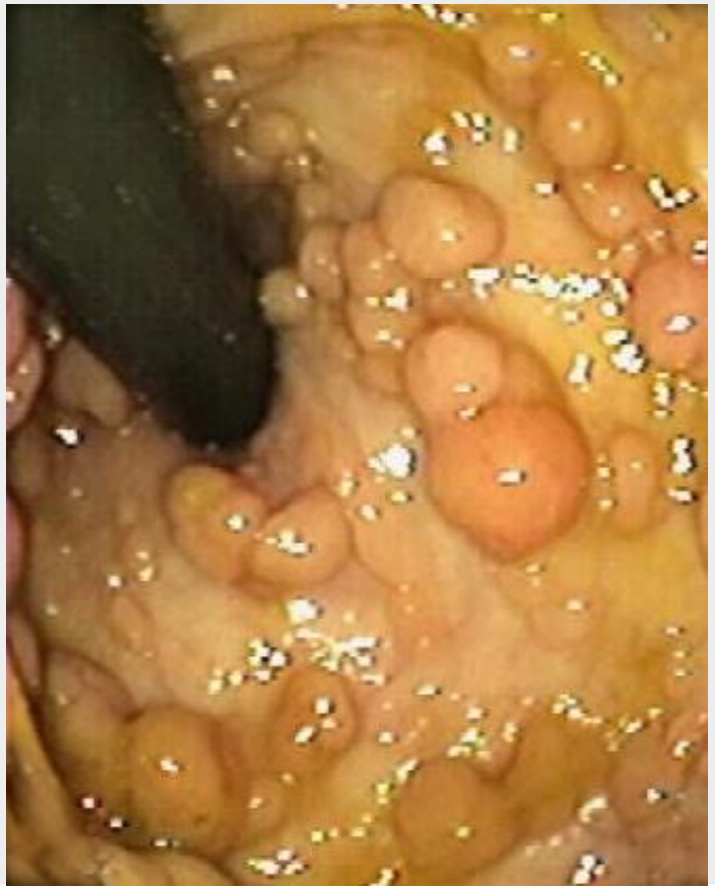
Familial Adenomatous Polyposis

Diagnosis

- Pathogenic *APC* gene variants in >90% with classic polyposis
- Prevalence 1/8000; Autosomal Dominance
- De Novo mutations: 30% of carriers have no family history

Clinical Features and CRC

- 100-1000s of adenomatous polyps
- The age at onset is variable:
  - by age 10 years: 15% of carriers manifest adenomas;
  - by age 20 years: 75%; and by
  - By age 30 years, 90% will have presented with FAP



Extracolonic Features of FAP

Extracolonic Tumor	Relative Risk	Absolute Lifetime Risk (%)
Desmoid	852.0	15.0
Duodenum	**330.8**	**5.0–12.0**
Thyroid	7.6	2.0
Brain	7.0	2.0
Ampullary	**123.7**	**1.7**
Hepatoblastoma	**847.0**	**1.6**
Gastric	**—**	**0.6**

Familial Adenomatous Polyposis

- **100% lifetime risk of CRC** if absence of intervention
  - In APC carriers, colonoscopy ~12 years
  - Proctocolectomy in late teens/young adults with annual endoscopic surveillance
- **80% with duodenal polyposis;** duodenal or periampullary cancer in 5- 12%
  - EGD every 1-3 years
- Surgical/endoscopic treatment do not completely eliminate the risk for future polyps
- Unmet need for pharmacologic agents to delay endoscopic or surgical interventions

MYH-Associated Polyposis

- Phenotype varies from “classic” to “attenuated”
  - Autosomal recessive; Base-excision repair
- CRC risks varied

  Monoallelic *MUTYH*: CRC risk near 2x above average

  Biallelic *MUTYH*: lifetime CRC risk of 80%
- Mean age of CRC: 45-56 years
  - Screening initiation 25-30 years
- Polyposis burden is variable
  - Attenuated phenotype (10-100 polyps)>> Classic polyposis (>100)

Hamartomatous Polyposis

- Peutz Jeghers, Juvenile Polyposis and Cowden
- Syndromes are rare
  - No evidence-based surveillance recommendations
- Increased risk of CRC and other cancers
  - Guidelines have been published based on retrospective and case series
- Cancer risks exceedingly high: ascertainment and selection bias

Peutz Jeghers Syndrome

- Clinical Criteria
  - ≥ 2 hamartomas
  - Mucocutaneous hyperpigmentation
  - Family history of Peutz Jeghers

- Germline pathogenic *STK11* gene variant
- Most cancers are GI: childhood UGI screening
- Lifetime cancer risk (all cancers): ~93%

Associated cancers	Cancer Risk	Surveillance	Initiation Age
Colorectum	39%	Colonoscopy: every 2–3 years	18 y
Breast	55%	Mammography or breast MRI: annually	25 y
Pancreas	36%	Endoscopic ultrasound or MRCP every 1-2 years	30 y
Stomach	29%	EGD: every 2-3 years	8 y
Lung	15%	No current recommendations	
Small bowel	13%	Small bowel imaging (capsule endoscopy, small bowel follow-through, CT or MRI enteroscopy): every 2-3 years	8 y
Endometrium/cervix Ovarian	9% 21%	Annual pelvic examination, Papanicolaou smear, and transvaginal ultrasound	18 y
Testicle	<1%	Annual testicular examination ± ultrasonography	10 y

Juvenile Polyposis

- Clinical Criteria
  - ≥ 3 juvenile polyps (colon)
  - Multiple gastric/small bowel juvenile polyps
  - Family history of juvenile polyps
- Germline pathogenic *SMAD2/BMPR1A* gene variant

Associated Cancer	Cancer Risk	Surveillance	Initiation Age
Colorectum	40-50%	Colonoscopy: annually until polyp free then every 2-3 years	15-18 y
Stomach	20%	EGD: annually when polyps are found otherwise every 2-3 years	15-18 y
Small intestine	<1%	There is currently no evidence to support screening	

Cowden Syndrome

- Clinical Criteria
  - Multiple hamartomas of gastrointestinal tract
  - Personal/Family history of breast, thyroid, or endometrial cancer
- Germline mutations in *PTEN* gene

Associated Cancer	Cancer Risk	Surveillance	Initiation Age
Breast	50%	Annual mammography or breast MRI	30-35 y
Thyroid	10%	Annual thyroid ultrasonography	18 y
Colorectum	16%	Colonoscopy every 3-5 years	35 y
Endometrium	30%	Biopsy/TVUS	30-35 y

Additional CRC susceptibility genes with clinical implications

Moderate Penetrance

- *APC* I1307K, *CHEK2,* Monoallelic *MUTYH*
- Colonoscopy start at age 40 years
- Surveillance: every 5 years

Rare Genes

- *POLE, POLD1, GREM1, AXIN2, NTHL2, MSH3*
- Colonoscopy start at age 25-30 years
- Surveillance: every 2-3 years if no polyps; annual if +polyps

Kastrinos et al, *Gastroenterology*, 2020

Summary: Current Strategies for Early GI Cancer Detection & Prevention

Colonoscopy

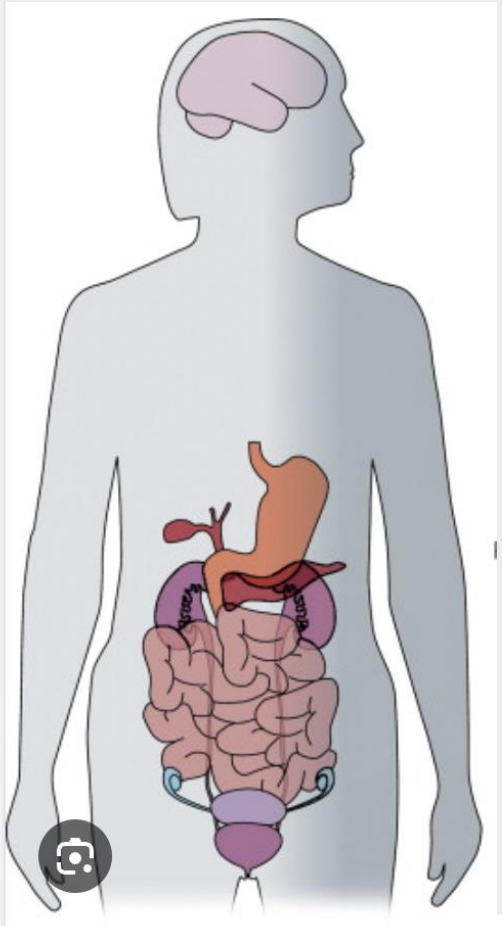
COLORECTAL

Lynch syndrome
FAP
MUTYH
Peutz Jeghers
Juvenile Polyposis

Endoscopic Ultrasound

PANCREAS*

Lynch syndrome
Peutz Jeghers



GASTRIC

Lynch syndrome
FAP/GAPPS
Peutz Jeghers
Juvenile polyposis
Li-Fraumeni

EGD

SMALL BOWEL*

Lynch syndrome
FAP
Peutz Jeghers
Juvenile polyposis

Video Capsule Endoscopy, Enteroscopy

* Includes radiographic imaging

Novel Prevention Strategies in Inherited CRC Syndromes:
Chemoprevention & Immunoprevention

Chemoprevention in FAP

COX inhibition most studied and used in FAP: Sulindac use variable; mostly studied as control arm/SOC

Eflornithine + sulindac*: decreases mucosal polyamines associated with adenomas

- Phase 3, randomized, double-blind trial
- N=171; randomized 1:1:1 ratio: 750 mg eflornithine, 150 mg sulindac, or both; once x 48 months
- Disease progression in 32% with combo, 38% with sulindac, and 40% with eflornithine

EGFR Inhibitors

- Erlotinib**: Phase 2 trial, single-arm, multi-center; N=46; 350 mg once weekly
  - Near 30% reduction in duodenal polyp burden; similar for colorectal polyps

Immunomodulators: inhibition JAK/STAT pathway

- Lorpucitinib: Phase 1b trial (NCT05014360)
  - Multi-center, open-label, single arm; Lorpucitinib twice daily for 24 weeks; N=42
- Guselkumab: Phase 1b; inhibition of IL 23/IL 17/JAK/STAT3 pathway (NCT05014360)
  - Multicenter, Randomized, Blinded, Placebo-controlled; 24 weeks; N=77
  - 3 arms: Guselkumab 100 mg SC, Guselkumab 300 mg SC, and placebo SC

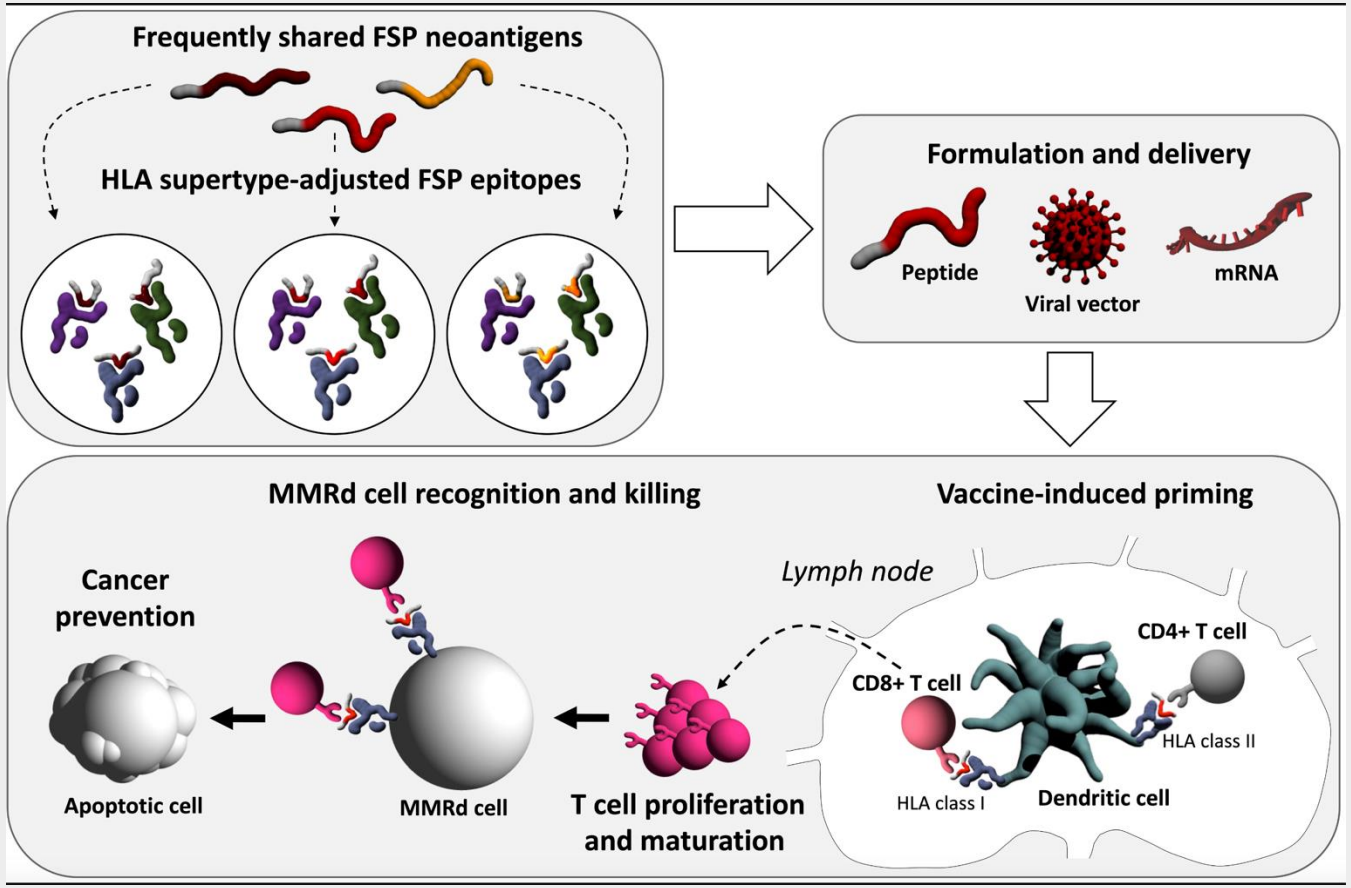
*Burke CA et al. *NEJM*, 2020
**Samadder NJ et al. *GUT* 2023

Chemoprevention in Lynch Syndrome: Aspirin and the CAPP2 Study

- Double-blind, randomized trial
- 861 patients: 600 mg aspirin daily or placebo
- Primary endpoint: development of CRC; Analysis was by ITT; outcomes monitored for 10 years
- ASA versus placebo: 9% (40/427) versus 13% (58/434) developed CRC
- Intention-to-treat: significantly reduced HR 0.65 (p=0.035) for ASA versus placebo
- 24 Lynch syndrome patients NTT with 600mg/day ASA to prevent 1 CRC
- Adverse events similar between both groups

Burn et al, *Lancet* 2020

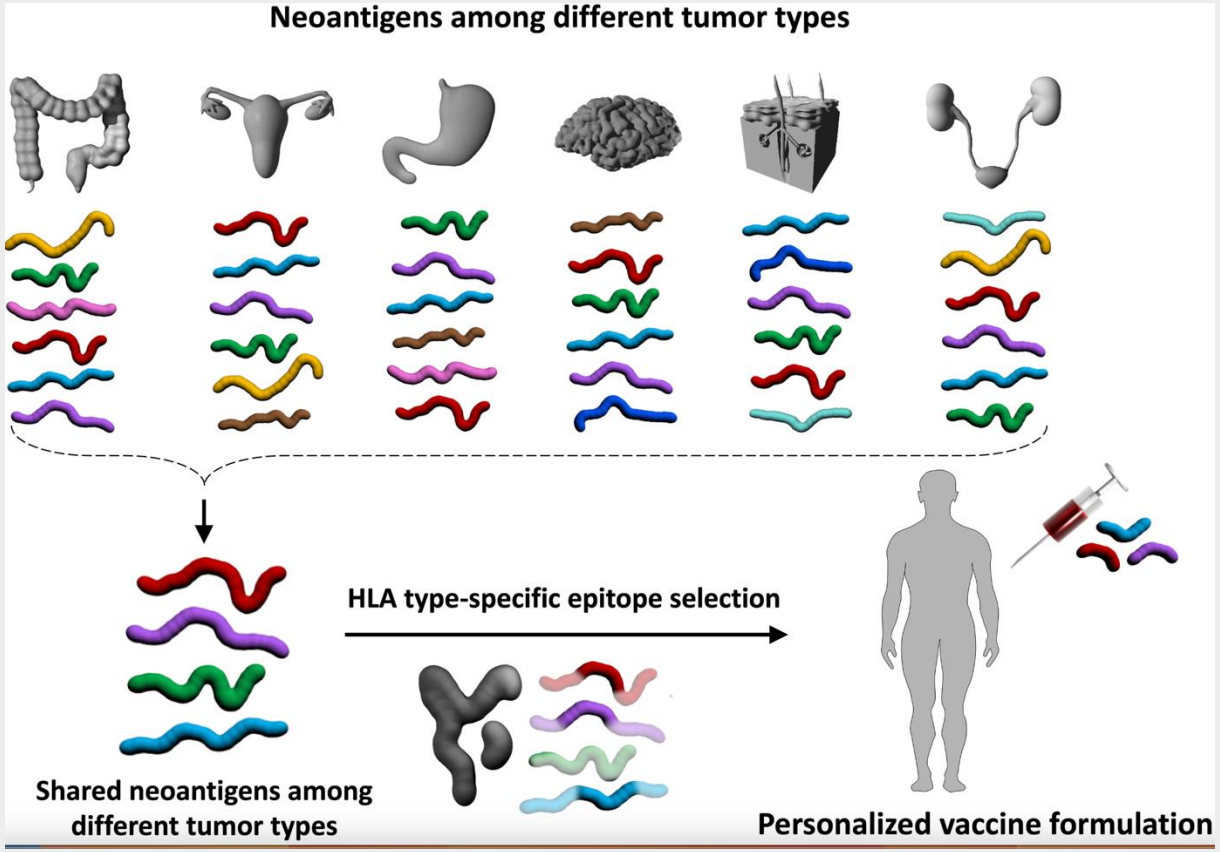
Vaccines for Cancer Interception: Immunoprevention in Lynch syndrome



- Lynch Syndrome tumors/premalignant lesions have a high number of frameshift mutations and express tumor associated antigens (TAAs)
- Vaccines can generate immune-mediated response against the TAAs
- Lynch syndrome specific vaccines may either prevent lesion formation, progression, or lead to regression

Sei S, et al. *Front. Oncol*. 2023

Personalized Vaccines for Multi-cancer Prevention in Lynch Syndrome



- Certain neoantigens are shared across different tumors
- Neoantigens are adjusted by an individual's HLA genotype
- Personalized vaccines with these shared neoantigens + HLA-genotype may allow for multi-cancer prevention without organ restriction

Sei S, et al. *Front. Oncol*. 2023

Vaccine Trials in Lynch syndrome: Nous-209 and Tri-Ad5

Nous-209 (NCT05078866)

- Phase 1 to assess safety and immunogenicity; N=45
- Vaccine contains 209 neoantigens expressed only in premalignant/malignant tissues of LS carriers

Tri-Ad5 (NCT05419011)

- Phase 2b trial to test safely and effectiveness; Randomized Control Trial; N=158
- Trivalent adenovirus-5 (Tri-Ad5) vaccines and IL-15 superagonist
- Vaccines containing tumor-associated antigens overexpressed in cancer cells (CEA/MUC/brachyury)
- Clinical endpoint: development of colonic neoplasms

Future Directions for the Early Detection of CRC in High-Risk Individuals

Individuals at High-Risk for GI Cancers: Current Strategies for Early Cancer Detection & Prevention

Colonoscopy

COLORECTAL

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Juvenile Polyposis

Endoscopic Ultrasound

PANCREAS*

Lynch syndrome
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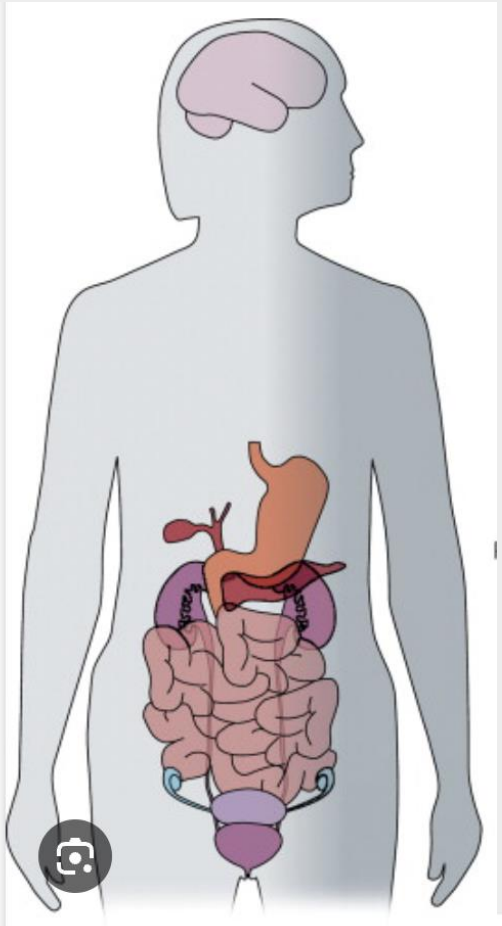

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Video Capsule Endoscopy, Enteroscopy

* Includes radiographic imaging

Limitations to Endoscopic Screening for HRI

30-50 years of intensive CRC surveillance among HRI

Invasive procedure and compliance

- Resource dependent
- Days off work, preparation, financial burden

Interval cancers can happen

- Biology versus quality of colonoscopy

Adherence to Genotype specific screening recommendations

- Evidence-based practice varies

Early Detection Biomarkers

Non-invasive tests are a potential alternative/complementary strategy to endoscopic screening tests

- Not currently incorporated into screening protocols for HRI

Progress begets challenges

- Commercially available early detection biomarkers tests used outside of clinical trials, make it difficult to assess their full impact

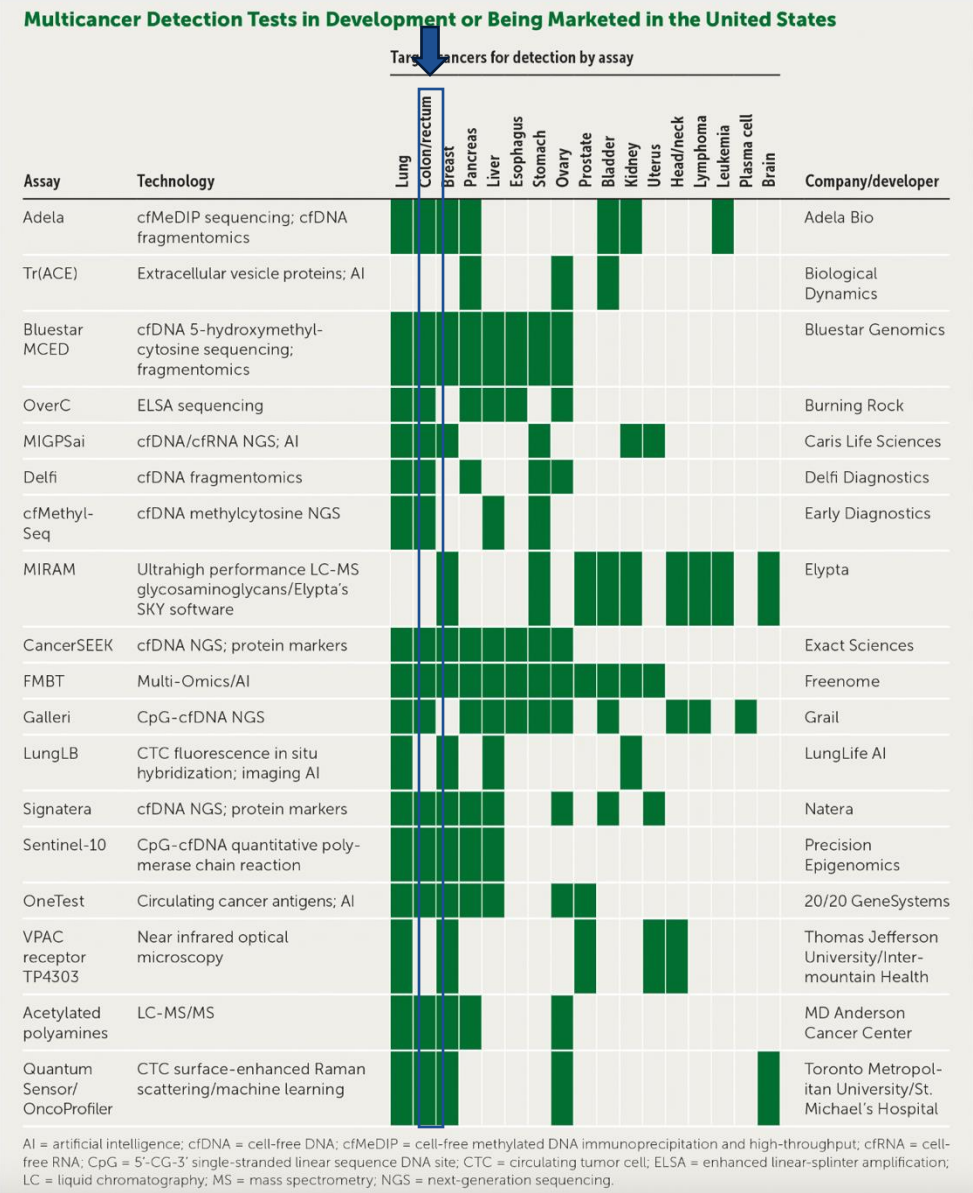
NCI's EDRN developed a framework for biomarker evaluation with 5 phases

- Final phase is to demonstrate that applying the test *achieves a mortality benefit*

Where are we now?

- There is limited data that evaluates blood-based biomarkers in HRI
- Current modalities under consideration for use in HRI
  - Stool vs. Blood-based Single Cancer vs. Multi-Cancer Early Detection Tests
    - Stool based FIT and mt-DNA
    - SCED : i.e., Guardant's Shield
    - MCED: i.e., Grail's Galleri

Non-Invasive Early Detection Screening Tests



Multicancer Detection Tests in Development or Being Marketed in the United States

Assay	Technology	Lung	Colon/rectum	Breast	Pancreas	Liver	Esophagus	Stomach	Ovary	Prostate	Bladder	Kidney	Uterus	Head/neck	Lymphoma	Leukemia	Plasma cell	Brain	Company/developer
Adela	cfMeDIP sequencing; cfDNA fragmentomics	■	■	■	■						■	■				■			Adela Bio
Tr(ACE)	Extracellular vesicle proteins; AI				■				■		■								Biological Dynamics
Bluestar MCED	cfDNA 5-hydroxymethyl-cytosine sequencing; fragmentomics	■	■	■	■	■	■	■	■										Bluestar Genomics
OverC	ELSA sequencing	■	■		■	■	■		■										Burning Rock
MIGPSai	cfDNA/cfRNA NGS; AI	■	■	■				■				■	■						Caris Life Sciences
Delfi	cfDNA fragmentomics	■	■		■			■	■										Delfi Diagnostics
cfMethyl-Seq	cfDNA methylcytosine NGS	■	■			■		■											Early Diagnostics
MIRAM	Ultrahigh performance LC-MS glycosaminoglycans/Elypta's SKY software			■				■		■	■	■		■	■	■		■	Elypta
CancerSEEK	cfDNA NGS; protein markers	■	■	■	■	■	■	■	■										Exact Sciences
FMBT	Multi-Omics/AI	■	■	■	■	■	■	■	■	■	■	■							Freenome
Galleri	CpG-cfDNA NGS	■	■		■	■	■	■	■		■			■	■		■		Grail
LungLB	CTC fluorescence in situ hybridization; imaging AI	■	■	■	■							■							LungLife AI
Signatera	cfDNA NGS; protein markers	■	■	■	■	■			■		■		■						Natera
Sentinel-10	CpG-cfDNA quantitative polymerase chain reaction	■	■	■	■	■													Precision Epigenomics
OneTest	Circulating cancer antigens; AI	■	■	■	■	■			■	■									20/20 GeneSystems
VPAC receptor TP4303	Near infrared optical microscopy	■	■	■						■			■	■					Thomas Jefferson University/Intermountain Health
Acetylated polyamines	LC-MS/MS	■	■	■	■				■										MD Anderson Cancer Center
Quantum Sensor/ OncoProfiler	CTC surface-enhanced Raman scattering/machine learning	■	■	■					■									■	Toronto Metropolitan University/St. Michael's Hospital

AI = artificial intelligence; cfDNA = cell-free DNA; cfMeDIP = cell-free methylated DNA immunoprecipitation and high-throughput; cfRNA = cell-free RNA; CpG = 5'-CG-3' single-stranded linear sequence DNA site; CTC = circulating tumor cell; ELSA = enhanced linear-splinter amplification; LC = liquid chromatography; MS = mass spectrometry; NGS = next-generation sequencing.

Doubeni CA, et al. *Am Fam Physician.* 2023

- Methylation-based markers
- Protein-based markers
- Exosome-based with miRNA

SCED versus MCED testing in HRI

False positives

- Lead to unnecessary procedures; ~ 40% of adults with a +MCED test signal had cancer

False negatives

- In some studies, the sensitivity for several cancer types was less than 50%

Overdiagnosis & overtreatment

- Depends on cancer type; diagnosis slow-growing cancers that never cause symptoms

- MCED tests have not been tested in large clinical trials
- Unclear if MCED tests reduce cancer mortality
- Not covered by insurance

Take Home Messages

- Numerous cancer syndromes associated with CRC
  - Genotype-specific endoscopic screening and risk-reducing strategies are recommended for CRC prevention
- Novel preventive strategies in FAP and Lynch syndrome
  - Chemo- and Immunoprevention
- Novel Screening Tests for Detection of GI Cancers
    - Validation studies needed in HRI to assess MCEDs/SCEDs
    - Evaluate integration of appropriate tests into current screening strategies
    - Assess cost-effectiveness and determine optimal screening strategies

Thank you

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