American Cancer Society®

NATIONAL COLORECTAL CANCER ROUNDTABLE

ACS NCCRT Blue Star Conversation

Cost-effectiveness of Lynch Syndrome Screening in Colorectal Cancer: Universal Germline vs Sequential Screening

August 26, 2026

Blue Star Conversations (BSCs) are ACS NCCRT members-only interactive virtual programs, covering new or hot button topics of interest in the colorectal cancer (CRC) space, and facilitated by ACS NCCRT staff and a high-level volunteer moderator.

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NATIONAL COLORECTAL CANCER ROUNDTABLE

Ground Rules

1 **Nonpartisan Commitment & Discussion Guidelines**

ACS/ACS CAN is a nonprofit, nonpartisan organization. We believe everyone should have a fair and just opportunity to prevent, detect, treat, and survive cancer. We therefore ask that you avoid partisan topics and opinions today.

2 **ACS National Roundtable Rules for Engagement**

Rules for engagement clarify the expectations for participation by members and representatives of the ACS NCCRT. Members are expected to respect and comply with these Rules and all other applicable ACS policies.

You can reference the Rules for Engagement anytime on our website.

3 **Confidentiality**

This session is being recorded. Please be mindful of our conversation and respectful of others' privacy. Do not identify or discuss specific patients by name.

Virtual Housekeeping

1. Please note the presentation is being recorded.

2. We want to hear questions from you via the chat at the bottom of the screen

3. Let’s get to know each other– put your name, what state you’re from, which organization you represent in the chat, and one emoji describing your summer so far

4. Don’t forget to complete our evaluation at the end of today’s call!

Moderator

Heather Hampel, MS, CGCC

Professor, Department of Medical Oncology & Therapeutics Research
Associate Director, Division of Clinical Cancer Genomics, City of Hope
Former ACS NCCRT Steering Committee Member
ACS NCCRT Priority Team Co-Chair

Learning Objectives

1. Appreciate the factors that contribute to the cost-effectiveness of Multi-Gene Panel Testing for all Colorectal Cancer Patients;

2. Understand changes to the 2026 NCCN Guidelines regarding Multi-Gene Panel Testing for all Colorectal Cancer; and

3. Know Options for Organizations to use Tumor Screening Instead of Multi-Gene Panel Testing to Screen Colorectal Cancer Patients for Lynch syndrome.

NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, & Gastric Version 1.2025

- Since 2022, NCCN Recommended genetic testing for all CRC patients dx <50
- Consider genetic testing for CRC patients dx ≥ 50

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

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RATIONALE, PROS, AND CONS OF MULTIGENE PANEL TESTING FOR LYNCH SYNDROME AND OTHER CANCER RISK GENES

Rationale:
The germline MGPT strategy is an alternative to tumor- and family history-driven selection of patients with CRC or EC for genetic testing, because it is more sensitive for identifying individuals with LS and other cancer risk genes than a strategy of selecting for germline testing based on family history and tumor-based criteria.

Pros	Cons
• Compared to genetic evaluation based on family history or tumor testing for evidence of dMMR, MGPT has: ‣ Comparable or even higher yield for identifying individuals with LS.[1,2,3,4] ‣ Higher yield for identifying individuals with a PV in a cancer risk gene. MGPT identifies a PV in 7.8%–16.0% of patients with CRC.[2,3,4,5] MGPT identified a PV in 9.2%–14% of patients with EC.[6,7,8,9,10,11] • Some of the PVs identified by MGPT are clinically actionable and inform screening and surveillance recommendations. • Identified PVs allow for subsequent family cascade testing and may allow for additional opportunities for early detection and prevention of cancer.[3,5,12] • A majority of individuals with a personal history of CRC or EC do not meet previous NCCN criteria for MGPT based on family history or tumor-based criteria.[3] • MGPT may simplify referral and testing for genetic evaluation. ‣ MGPT is augmented by, but not dependent on knowledge of family history or tumor characteristics. ‣ Steps required for evaluating for a genetic syndrome are simplified.	• Based on current evidence and available therapies, a germline MGPT result alone does not inform CRC or EC treatment decision-making. ‣ Presence of a PV in an LS-associated mismatch repair (MMR) gene is not sufficient to initiate immune checkpoint blockade therapy based on MSI-high (MSI-H) status. Tumor-based microsatellite instability (MSI) testing or immunohistochemistry (IHC) testing for expression of the MMR proteins are required for determining eligibility for immune checkpoint blockade therapy based on presence of dMMR.[13] • PVs in cancer risk genes for which clinical management is uncertain or not informed by well-established evidence will be identified. • Many individuals will have a VUS. ‣ 29%–63% of individuals with CRC may have a VUS at time of MGPT depending on the size of the gene panel.[2,3,4,5] • Proportion of patients with a VUS may be higher among people from particular racial/ethnic groups, especially with utilization of large multigene panels, potentially increasing burden of uncertain results on these populations.[5,14,15,16] • Capacity to offer MGPT to all patients with CRC or EC and CRC or EC survivors is uncertain. ‣ In the United States, 150,000 individuals are diagnosed with CRC annually, and there are currently 1.5 million CRC survivors; 66,200 individuals are diagnosed with EC annually, and there are >600,000 EC survivors. ‣ It is unclear if there is sufficient capacity to deliver pre-test informed consent and appropriate counseling to all individuals with PVs and VUSs, as well as negative results. Tumor registry data from 2013–2019 indicate that genetic testing rates among patients with CRC and EC are 5%–6%.[17] • Results may not return in time to inform surgical decision-making.

Note: All recommendations are category 2A unless otherwise indicated.

References

HRS-A
1 OF 3

NCCN Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, & Gastric Version 1.2025

- Many caveats

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NCCN Guidelines Version 1.2025
Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

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RATIONALE, PROS, AND CONS OF MULTIGENE PANEL TESTING FOR LYNCH SYNDROME AND OTHER CANCER RISK GENES

Challenges and Evidence Gaps:

- Impact of MGPT on subsequent cascade testing and evaluation for family members is uncertain.
  - Currently available studies of evaluating MGPT for patients with CRC report cascade testing occurred in 16% to 65% of families.[3,5]
- Cost effectiveness is uncertain. There is no recent U.S.-based study using current testing costs. A Swiss study suggested MGPT was cost-effective relative to tumor-based screening for LS.[18]
- Yield in individuals with CRC unselected based on other characteristics is uncertain.
- Most currently available studies have potential selection bias that might overestimate the yield of MGPT across the spectrum of all patients with CRC.
- Spectrum of PVs occurring in cancer risk genes among people from racial and ethnic groups requires additional research.

Test Selection:

- For patients with CRC:
  - Germline MGPT should include at minimum the following CRC and/or polyposis risk-associated genes: *APC*, *BMPR1A*, *EPCAM*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *PTEN*, *SMAD4*, *STK11*, and *TP53*. Management recommendations for individuals with a PV in these genes are described in GENE-1.
  - Germline MGPT with the following genes that have also been associated with increased risk for polyposis and/or CRC may also be considered: monoallelic PVs in *AXIN2*, *GREM1*, *POLE*, and *POLD1*, and biallelic PVs in *MSH3*, *MLH3*, *MBD4*, and *NTHL1*. Management recommendations for individuals with a PV in these genes are described in GENE-1.
  - The following additional genes are found on some genetic testing panels: *ATM*, *BLM*, *CHEK2*, *FOCAD*, *GALNT12*, *RNF43*, and *RPS20*. Management recommendations for some of these genes are listed in GENE-1.
- For patients with EC:
  - Germline MGPT should include at minimum the following EC risk-associated genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *PTEN*, and *BRCA1/2*. Management recommendations for individuals with a PV in these genes are described in GENE-1.
  - Germline MGPT with the following genes that have also been associated with increased risk for EC may also be considered: *POLD1*, *POLE*. See Comments section on GENE-11 for additional information.
- Selection of a panel and decision to retest that includes additional genes beyond these minimal sets should be based on considerations such as age at presentation, polyp phenotype, and personal and family history of cancer, as well as patient and provider preference. For a list of additional genes that may confer a risk for cancers and any associated recommendations, see tables in Cancer Risk Management Based on Genetic Test Results (GENE-1) and in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate.

Today's Presenters

Xavier Llor, MD, PhD

Professor of Medicine
Director, GI and Pancreatic Cancer Prevention Program, Digestive Diseases, Yale School of Medicine
Former ACS NCCRT Steering Committee Member
ACS NCCRT Priority Team Co-Chair

ACS NCCRT Blue Star Conversation

Cost-effectiveness of Lynch Syndrome Screening in Colorectal Cancer: Universal Germline vs Sequential Screening

Xavier Llor, MD, PhD
Director, Gastrointestinal and Pancreas Cancer Prevention Program
August 26, 2026

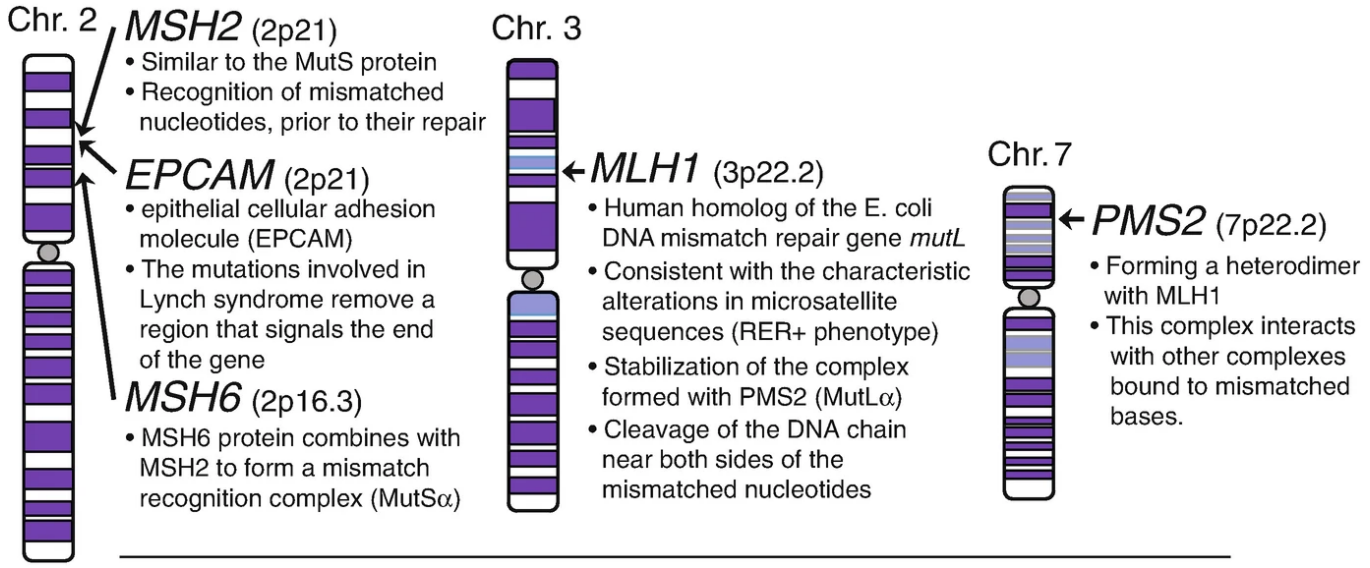
Yale SCHOOL OF MEDICINE

Disclosure Information

- Parabilis Medicines (consultant)
- International Consulting Associates-Centers for Medicare and Medicaid Services (consultant)

Lynch Syndrome

- Most common inherited GI cancer syndrome
- 1/279 individuals (0.36%) (>1M Americans) have a germline MMR gene mutation, causing Lynch syndrome.
- Autosomal dominant multicancer syndrome[1]



Gene	MIM	Locus	No.of exon	CDS (nt)	Product no. of amino acid	MW (kDa) of protein
MLH1	*120436	3p22.2	19	2218	756	84.6
MSH2	*609309	2p21	16	2802	934	104.7
MSH6	*600678	2p16.3	10	4080	1360	152.8
PMS2	*600259	7p22.1	15	2586	862	95.8
EPCAM	*185535	2p21	9	942	314	35

[1]Win AK. *et al.* Cancer Epidemiol Biomarkers Prev. 2017 March ; 26(3): 404–412

Tamura, K. (2020). Molecular Mechanism of Lynch Syndrome. In: Tomita, N. (eds) Lynch Syndrome. Springer, Singapore.

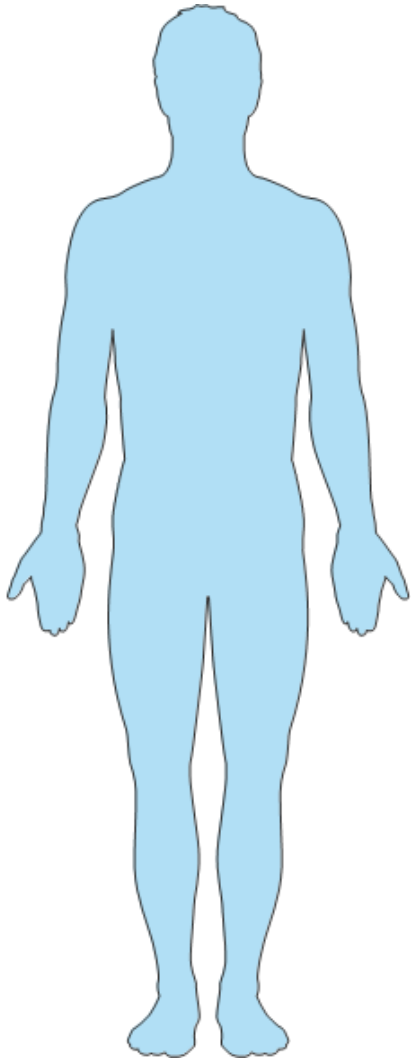
Cumulative Cancer Risk at Age 80

Colorectal
MLH1: 46-61%
MSH2: 33-52%
MSH6: 10-44%
PMS2: 8.7-20%

Small bowel
MLH1: 0.4-11%
MSH2: 1.1-10%
MSH6: <1-4%
PMS2: 0.1-0.3%

Pancreas
MLH1: 6.2%
MSH2: 0.5-1.6%%
MSH6: 1.4-1.6%
PMS2: No change

Gastric
MLH1: 5-7%
MSH2: 0.2-9%
MSH6: <1-7.9%
PMS2: Unclear



Endometrial
MLH1: 34-54%
MSH2: 21-57%
MSH6: 16-49%
PMS2: 13-26%

Ovarian
MLH1: 4-20%
MSH2: 8-38%
MSH6: <1-13%
PMS2: 1.3-3%

-Skin
-Brain

Renal pelvis and/or ureter
MLH1: 0.2-5%
MSH2: 2.2-28%
MSH6: 0.7-5.5%
PMS2: <1-3.7%

Bladder
MLH1: 2-7%
MSH2: 4.4-12.8%
MSH6: 1.0-8.2%
PMS2: <1-2.4%

Implications of diagnosing Lynch syndrome

- **Implementation of cancer preventive and surveillance measures**
  Decrease in morbidity and mortality

  - 1. **CRC surveillance**: Colonoscopy every 1-3 years
  - 2. **Upper GI tract surveillance**: EGD every 2-3 years
  - 3. **Uterine/ovarian cancer surveillance and prophylactic surgery:** Endometrial biopsy yearly. Transvaginal US in postmenopausal women. TH+BSO after childbearing age
  - 4. **Pancreas cancer surveillance**: alternating EUS with MRI yearly
  - 5. **Skin cancer surveillance**: Full body skin exam yearly (sebaceous adenomas/ carcinomas, keratoacanthomas)
  - 6. **Urothelial cancer surveillance**: UA (RBCs) yearly. Cystoscopy, Renal US

Implications of diagnosing Lynch syndrome

- **Chemoprevention and Immunoprevention/cancer interception:**
  - Daily 80 mg aspirin (CAPP3 trial)[1]
  - Vaccine: Eg: Nous-209 neoantigen (Nouscom Inc.) Lynch syndrome vaccine: adaptive immune activation against mismatch-repair–deficient neoantigens[2]

- **Cascade testing: Testing other family members for the familial mutation**

- **Prevent transmission to descendants: IVF and pre-implantation genetic diagnosis**

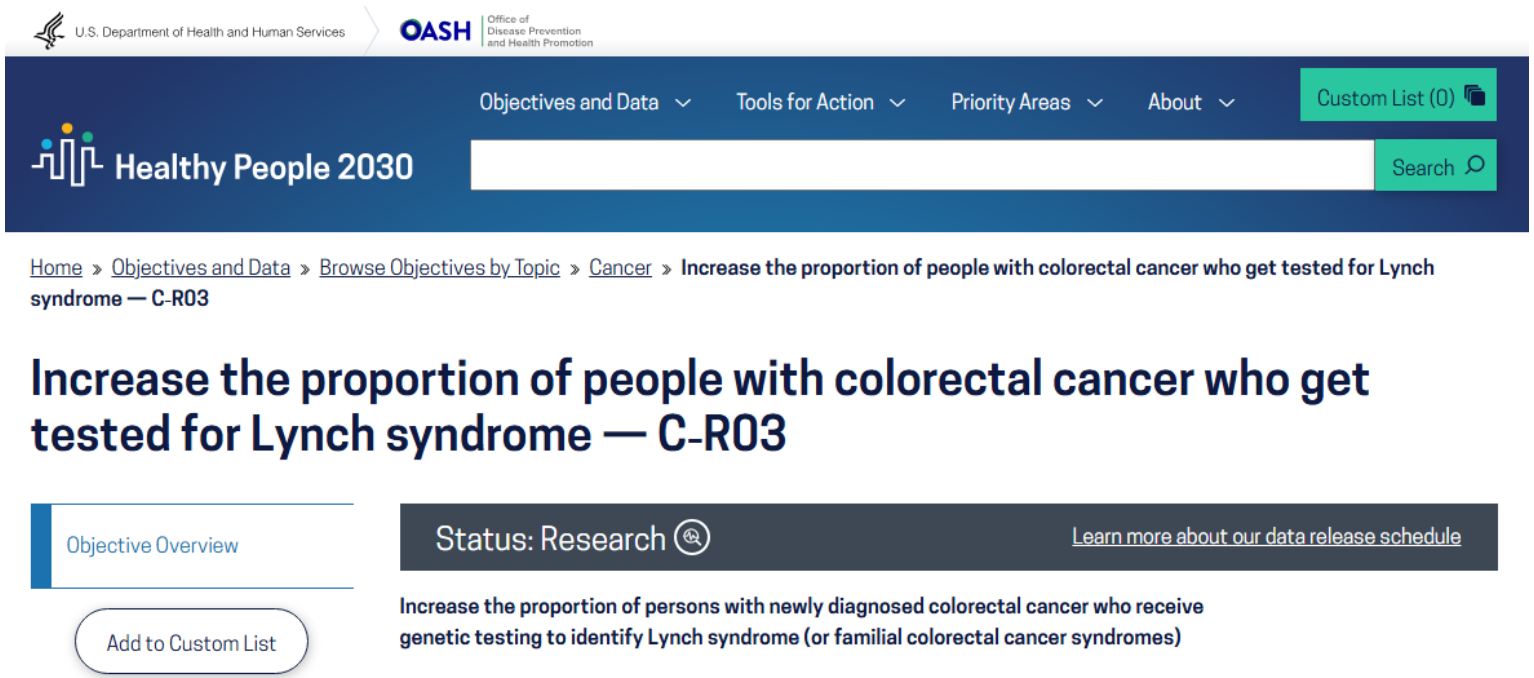
[1]Burn J. et al. Lancet Gastroenterol Hepatol. 2026 (9): 760-774

[2]D'Alise et al. Nat Med 2026 Issue 3 Pages 1002-1011

A Public Health Priority

Healthy People 2020

US Dep of Health and Human Services



https://odphp.health.gov/healthypeople/objectives-and-data/browse-objectives/cancer/increase-proportion-people-colorectal-cancer-who-get-tested-lynch-syndrome-c-r03

Identifying individuals for Lynch syndrome testing

Published in final edited form as:
Gastroenterology. 2020 March ; 158(4): 1159–1161. doi:10.1053/j.gastro.2019.11.297.

Low Rates of Genetic Counseling and Testing in Individuals at Risk for Lynch Syndrome reported in the National Health Interview Survey

Nolan Faust, M.D.[1,*], Charles Muller, M.D.[2,*], Joshua Prenner, B.A.[3], Sang Mee Lee, Ph.D.[4], Sonia S. Kupfer, M.D.[2]

- US National Health Interview Survey (NHIS): Only 8.4% of patients who qualified for genetic testing to rule out Lynch syndrome were recommended testing and 6.7% were finally tested

Low testing rates: barriers and solutions

- Low testing rates are due to a combination of factors[1]:
  - Lack of awareness among clinicians
  - Complex genetic testing guidelines
  - Clinician's unconscious bias
  - Slow implementation of streamlined assessment and testing processes

[1]Frey M. K., *et al. Gynecol Oncol* 2023 Vol. 173 Pages 22-30

Genetic testing criteria to evaluate for Lynch syndrome

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CRITERIA FOR TESTING FOR LYNCH SYNDROME[n]

Testing is clinically indicated in the following scenarios:	
• Known LS PV in the family • Personal history of an LS-related cancer (CRC, EC, or other[e]) and any of the following: ▸ Diagnosed <50 y[o,p] ▸ A synchronous or metachronous LS-related cancer[e] regardless of age ▸ 1 first-degree or second-degree relative with an LS-related cancer[e] diagnosed <50 y ▸ ≥2 first-degree or second-degree relatives with an LS-related cancer[e] regardless of age • Family history[q] of any of the following: ▸ ≥1 first-degree relatives with a CRC or EC diagnosed <50 y ▸ ≥1 first-degree or second-degree relatives with a CRC or EC and a synchronous or metachronous LS-related cancer[e] regardless of age ▸ ≥2 first-degree or second-degree relatives with LS-related cancers[e] including ≥1 diagnosed <50 y ▸ ≥3 first-degree or second-degree relatives with LS-related cancers[e] regardless of age • Increased model-predicted risk for LS ▸ An individual with a ≥5% risk of having an MMR gene PV based on predictive models (ie, $PREMM_5$, MMRpro, MMRpredict) ◊ Individuals with a personal history of CRC and/or EC with a $PREMM_5$ score of ≥2.5% should be considered for MGPT. ◊ For individuals without a personal history of CRC and/or EC, some data have suggested using a $PREMM_5$ score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.	Strategies for Testing for LS (LS-1)
• Personal history of CRC, EC, or of other tumor with MMR deficiency determined by polymerase chain reaction (PCR), next-generation sequencing (NGS), or IHC diagnosed at any age[r,s] • Personal history of a P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline[t,u]	Additional tumor-based testing (LS-A) OR Germline MGPT for LS and other hereditary cancer syndromes[z] [Strategies for Testing for LS (LS-1)]

Criteria based on:

-Known PV in the family

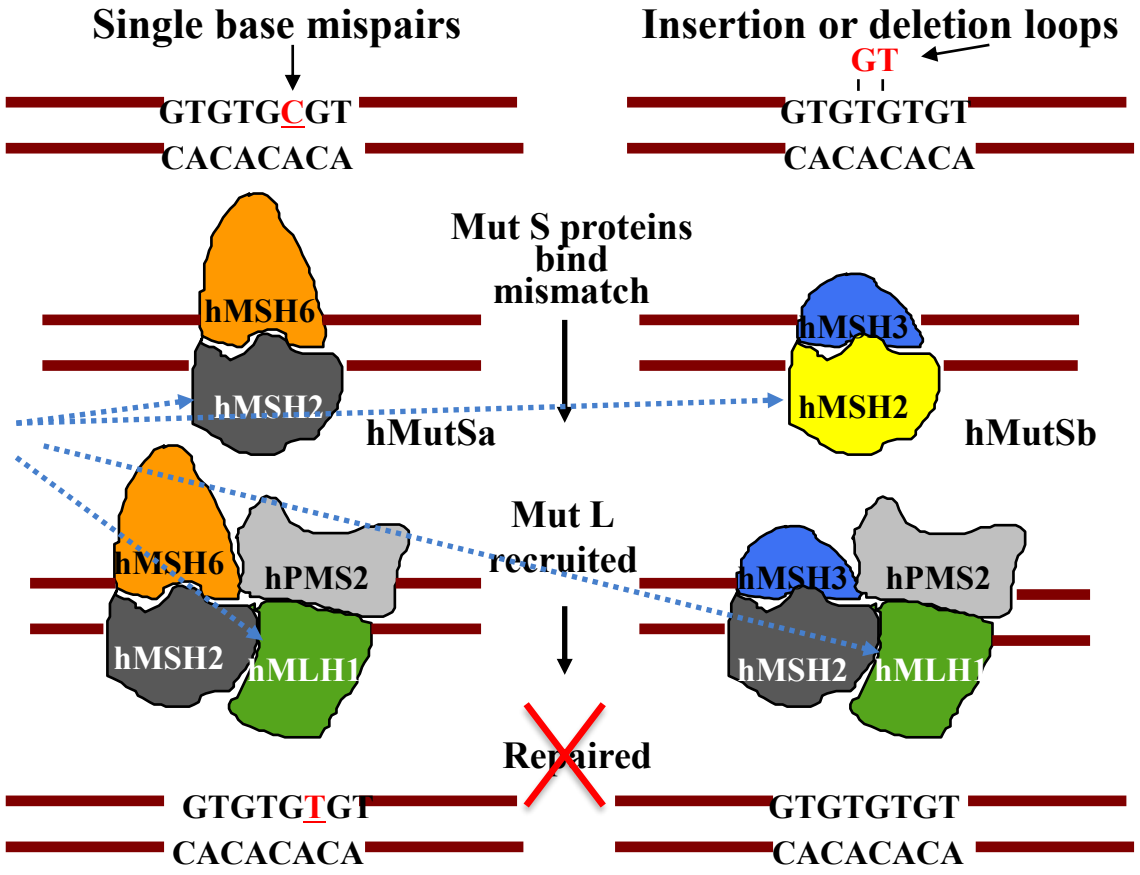
-Personal history of cancer/ family history of cancer

-Evidence of MMR deficiency in tumors

1. Patient information: Sex: Male Female
Current age (years)
Has the patient had colorectal cancer? No Yes
Has the patient had any other Lynch syndrome-associated cancer?
Other Lynch syndrome-associated cancers include ovary, stomach, small intestine, urinary tract/bladder/kidney, bile ducts, brain, pancreas, and sebaceous gland skin tumors. No Yes
2. Relatives: First-degree
First-degree relatives include parents, siblings, children, only from affected side of family. How many first-degree relatives have had colorectal cancer? None One Two or more
How many first-degree relatives have had endometrial (uterine) cancer? None One Two or more
Have any first-degree relatives had other Lynch syndrome-associated cancers?
Other Lynch syndrome-associated cancers include ovary, stomach, small intestine, urinary tract/bladder/kidney, bile ducts, brain, pancreas, and sebaceous gland skin tumors. No Yes
3. Relatives: Second-degree
Second-degree relatives are grandparents, grandchildren, aunts, uncles, nieces, nephews, only from affected side of family. How many second-degree relatives have had colorectal cancer? None One Two or more
How many second-degree relatives have had endometrial (uterine) cancer? None One Two or more
Have any second-degree relatives had other Lynch syndrome-associated cancers?
Other Lynch syndrome-associated cancers include ovary, stomach, small intestine, urinary tract/bladder/kidney, bile ducts, brain, pancreas, and sebaceous gland skin tumors. No Yes

Tumor testing to screen for Lynch syndrome

Lynch Syndrome mutations in MMR genes:
- *MLH1*
- *MSH2*
- *MSH6*
- *PMS2*



Courtesy Dr. A. Goel

LS MMR-deficient tumors:

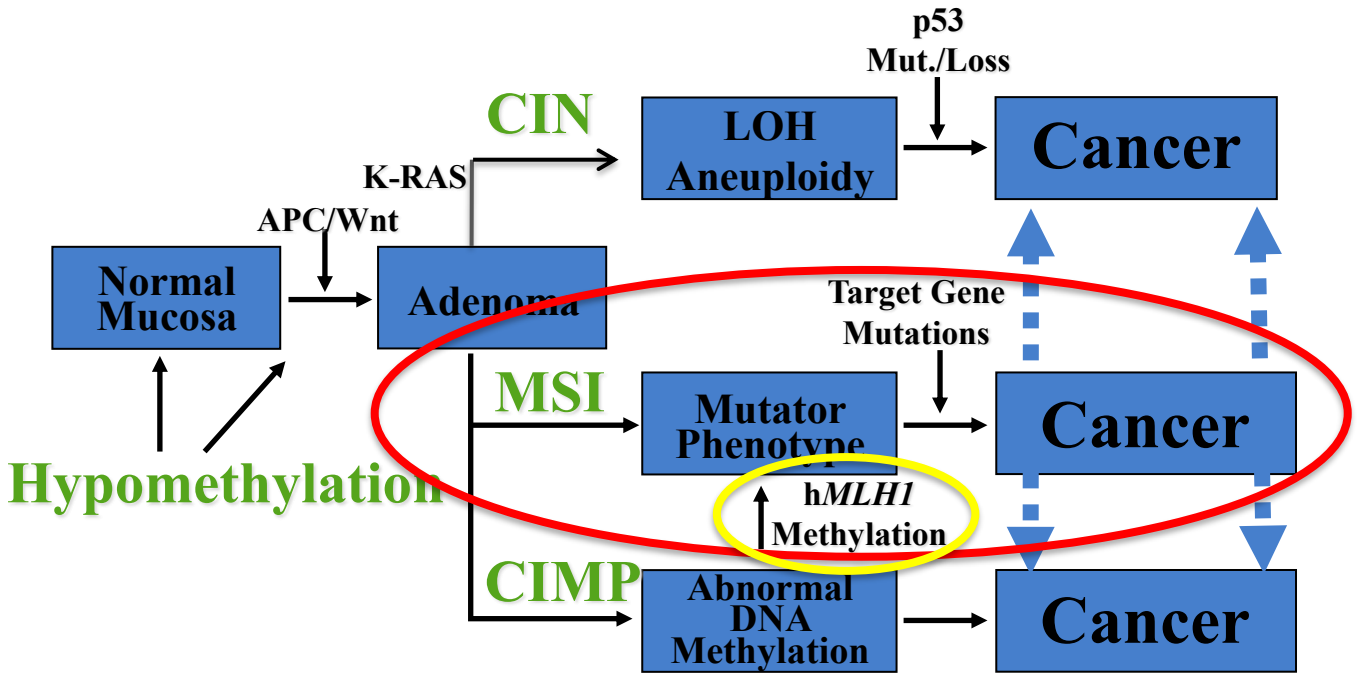
-Germline mutation in one allele

-Somatic inactivation of the second allele through mutation or promoter region methylation

↓

Loss of protein expression on IHC and MSI

MSI carcinogenic pathway



- About 15-20% of all GI and endometrial adenocarcinomas are MSI

  -About 1/3 of MSI tumors are due to LS
  -About 2/3: Somatic promoter methylation of *MLH1* *, somatic biallelic mutations in a MMR gene

*Almost all have a positive methylation assay; >60% have *BRAF* V600E mutation.

LS tumors: no *MLH1* methylation, no *BRAF* V600E PVs

Goel et al., Gastroenterology, 2007

Recommended tumor testing

- Recommended universal tumor testing for MMR deficiency (MSI and/or IHC) at the time of cancer diagnosis of all LS-related cancers* (+ *BRAF* V600E mutation/*MLH1* promoter methylation analysis)

*All GI adenocarcinomas, bladder/urothelial, adrenocortical, brain (glioblastoma, astrocytoma), sebaceous neoplasms

Identifying individuals for Lynch syndrome testing based on tumor testing

- **Implementation <50% of CRC in North America[1], 56% in 2017[2]**
- **Even when implemented, only 29.5% of individuals with MMR-deficient tumors underwent genetic testing[3]**

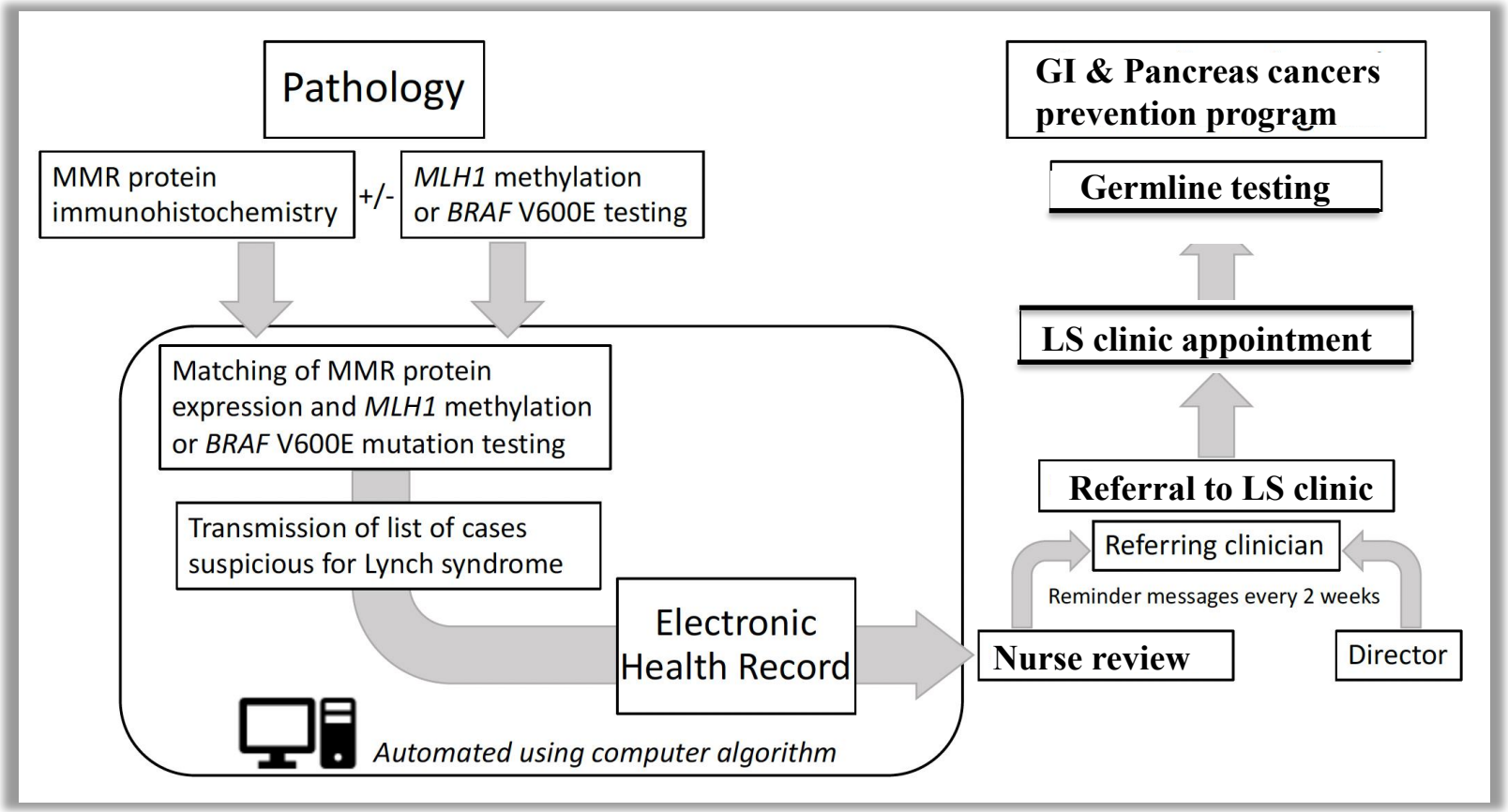
- [1] *Jain A, Shafer L, et al. Dig Dis Sci 2019;64:3489–501.* Survey practicing gastroenterologists through the CAG and the ACG
- [1] *Mittal C, et al. Dig Dis Sci 2020;65:3305–15.* Two large Veterans Affairs medical centers
- [1] *Shaikh T, et al. JAMA Oncol 2018;4:e173580.* National Cancer Database
- [2] Papke DJ, et al. 2022 Sep 2;31(9):1746-1751. National Cancer Database
- [1,3] *Muller C et al. Clin Gastroenterol Hepatol 2018;16:1911–8.* Four large academic centers

YNHH

	Patients (1/2012-5/2015) with MMR deficient CRC: n=29
CG referral among requiring evaluation	8/29 (27.59%)
Seen by CG among referred	8/29 (27.59%)
LS diagnosis	2/8 (25.0%)

Systematic approach: CLEAR-LS Intervention: Closed Loop Enhanced Assessment and Referral for Lynch Syndrome

Partnership with Yale Pathology



- Automated search of tumors:
  - -MMR deficient: abnormal IHC
  - -Mutated at *BRAF V600 E*
  - -*MLH1* promoter methylation
- Patients with MMR tumor with wild type *BRAF*V600 E or unmethylated *MLH1* selected for automated message to LS clinic
- LS clinic reach out to surgeon for reminder of referral 2 weeks after Dx. Two attempts and third personal message by clinic director
- Report: June 2015-January 2021

Singh, V. *et al. J Med Genet.* 2023, 6: 533-9

CLEAR-LS Intervention: Increased LS diagnosis by 50%

	Intervention cohort, N=76 (%)			Adjusted *p* value
	Referral prior to reach out (%)	Referral after reach out (%)	Total (%)	
CG referral among eligible	38/76 (50.00)	32/76 (42.10)	70/76 (92.11)	*<0.0001*
Seen by LS clinic among referred	32/38 (84.2)	20/32 (62.5)	52/70 (74.29)	*<0.0001*
LS diagnosis	9/32 (28.12)	4/20 (20.00)	13/52 (25.0)	*1.0000*

- The intervention resulted in:
  - -Referral rate of 92.11% (baseline 50%)
  - -Seen and tested among referred: 74.29%
  - -Increased LS diagnosis by 50%

Singh, V. *et al. J Med Genet.* 2023, 6: 533-9

CLEAR-LS Intervention: similar impact NHW vs others

Appropriate referral to Lynch syndrome clinic placed				
Race/Ethnicity*	Number of patients (%)	Original cohort (%)	Intervention cohort (%)	Adjusted P-value
NHW	57/100 (57)	6/24 (25)	51/76 (67.1)	<0.001
Other	21/29 (72.4)	2/5 (40)	19/24 (79.2)	0.193
Adjusted P-value			0.376	
Patients seen by Lynch syndrome clinic among the ones referred				
Race/Ethnicity*	Number of patients (%)	Original cohort (%)	Intervention cohort (%)	Adjusted P-value
NHW	46/75 (61.3)	6/24 (25.0)	40/51 (78.4)	<0.001
Other	13/24 (54.2)	2/5 (40)	11/19 (57.9)	0.629
Adjusted P-value			0.193	

*NHW: 79.1% Other: 11.8% African American; 6.7% Hispanics; 2.2% Asians

Referral and genetic testing uptake:

- No significant differences in referral rates
- No significant differences in evaluation and testing

Systematic approaches often have a disproportionately positive effect on underserved populations: can tackle unconscious bias

Singh, V. *et al. J Med Genet.* 2023, 6: 533-9

CLEAR-LS Intervention: Summary

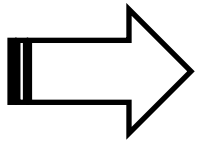
- Testing among qualifying individuals reached 74% with CLEAR-LS intervention
- 26% did not get tested, yet every single CRC underwent IHC +/- *MLH1* methylation/*BRAF* V600 E testing

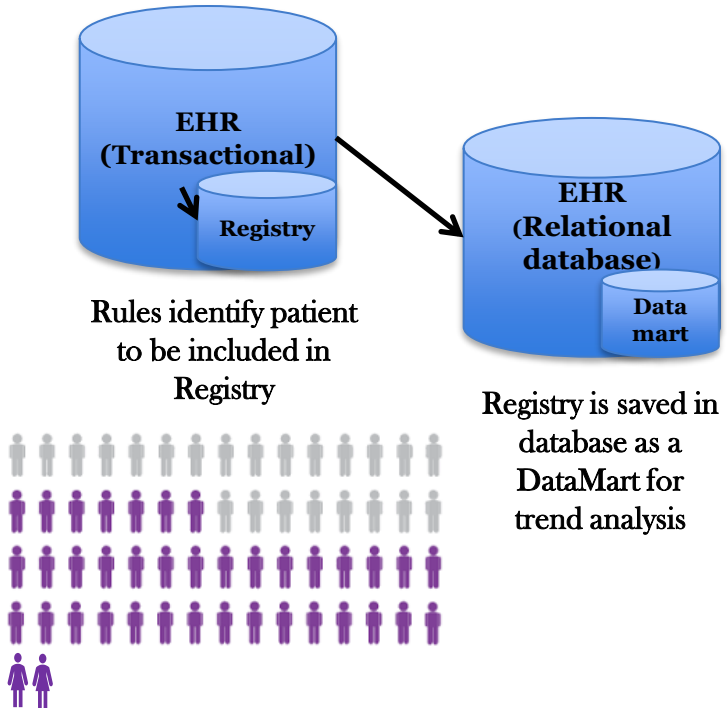
Singh, V. *et al. J Med Genet.* 2023, 6: 533-9

How are we doing, and how can we increase the detection of Lynch syndrome and other hereditary cancer syndromes?

- Can we do so by leveraging already available information in the EHR to help identify candidates for genetic testing?

Manual, clinician-based identification of at-risk individuals

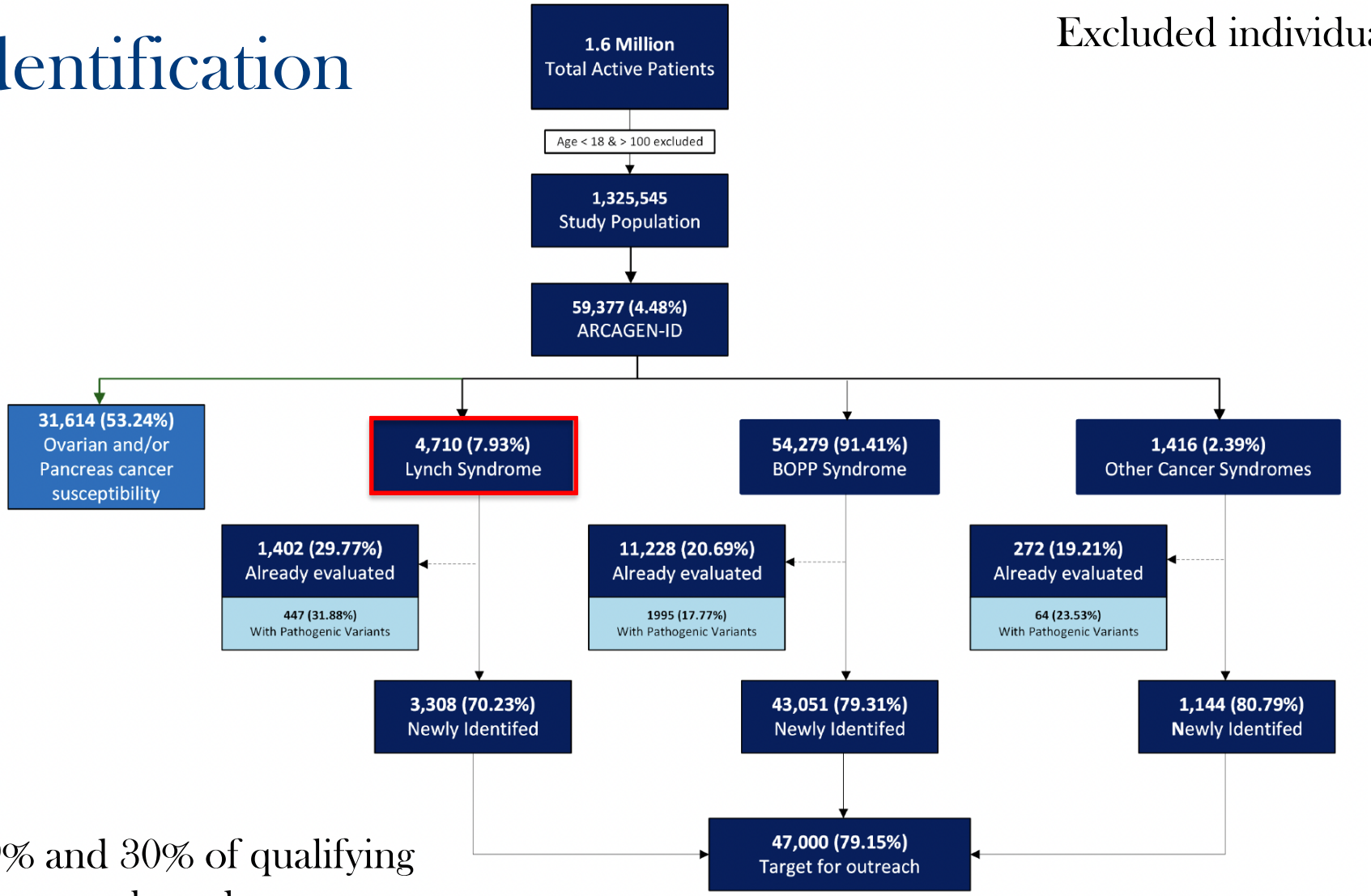




Goal: develop a guideline-driven tool integrated with the electronic health record (EHR) that can automatically process readily available information to compute a cancer risk assessment and thus identify individuals who qualify for hereditary cancer-based genetic testing

ARCAGEN-ID: Patient identification

Excluded individuals <18 and >100



Only between 19% and 30% of qualifying individuals had been evaluated

Singh, *et al. J Med Genet.* 2025 Jun 24;62(7):457-463

Deficient Diagnosis in the real-world

- Most individuals who qualify for genetic testing to rule out Lynch syndrome and other cancer syndromes are not being identified
- It is very difficult for most clinicians to suspect cancer genetic syndromes unless penetrance in the family is extremely high
- Even in that case, most clinicians do not recognize current testing criteria
- Opportunity to develop robust systems to help identify individuals at-risk

Singh, *et al. J Med Genet.* 2025 Jun 24;62(7):457-463

Diagnosis in the real-world

- Low compliance with CRC MMR testing (<60%) and even lower genetic testing (<50%) in the US

- Factors contribute to attrition:
  - Complexity of the multi-step process
  - Clinicians may overlook referring for genetic testing in MMR-deficient tumors
  - Newly diagnosed cancer patients often face overwhelming appointments and treatments, making genetic testing a lower priority

- Compliance rates are even lower for African American and Hispanic patients compared to non-Hispanic White patients

Would up-front germline testing be more cost-effective for LS diagnosis?

Jain A et al. Dig Dis Sci 2019;64(12):3489-3501
Mittal C et al. Dig Dis Sci 2020;65(11):3305-3315
Shaikh T et al. JAMA Oncol 2018;4(2):e173580
Muller C et al. Clin Gastroenterol Hepatol 2018;16(12):1911-1918

Upfront germline testing

- The National Comprehensive Cancer Network (NCCN) has been recommending upfront germline testing for patients under the age of 50 only

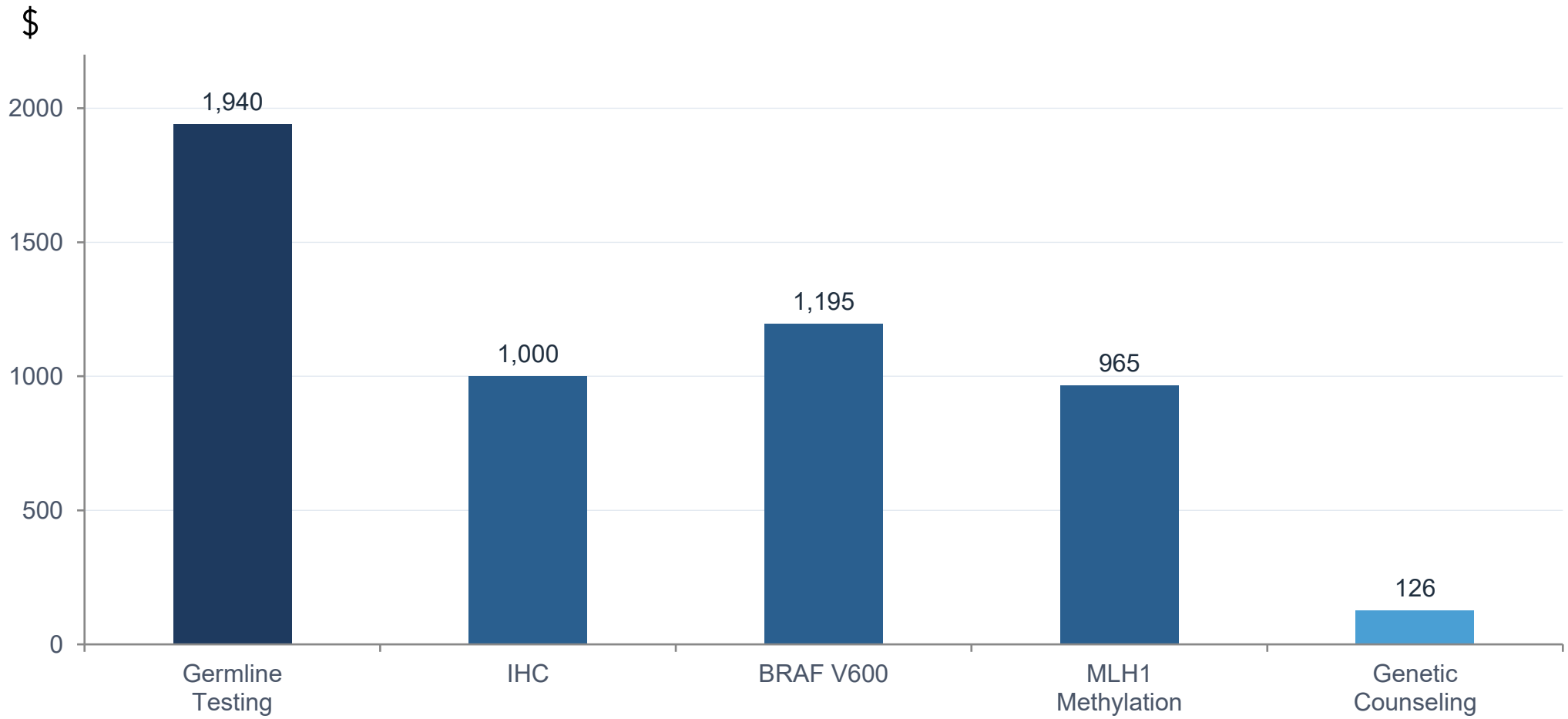
- Upfront germline testing was previously reported to be cost-ineffective in the United States
  - Absence of consideration of the real-world diagnostic attrition (not available)
  - Studies are >10 years old: dramatic decrease in germline testing over the last few years

NCCN Guidelines® Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, Esophageal, Gastric V. 1 .2026

Hao et al. *J Pers Med.* 2021;11(12):1284.
Wang et al. *J Oncol Pract.* 2012;8:e24s-30s.

Ladabaum et al. *Ann Intern Med.* 2011;155(2):69-79.
Barzi et al. *J Natl Cancer Inst.* 2015;107(4):djv005.

Cost Comparison by Test Type: YNHH Institutional costs 2023



Cost-effectiveness evaluation

Strategies for Lynch syndrome in incident colorectal cancer patients:

1) Current standard of care (sequential screening with a lower testing rate) versus

2) Optimal standard of care (sequential screening with a higher testing rate)-**CLEAR-LS** versus

3) Upfront germline testing

Goshua Lab
Decision Science in Clinical Medicine

Methods: parameters

Design:	Three-step cohort simulation
Population:	Probands with newly diagnosed with colorectal cancer
Comparators:	1a) IHC followed by germline testing 1b) IHC and *MLH1* methylation followed by germline testing 1c) IHC and *BRAF* V600E mutation followed by germline testing 2) IHC followed by germline testing with CLEAR-LS 3) Upfront germline testing
Time horizon:	Lifetime
Perspective:	US healthcare system

Ito S & Xicola RM et al. *Clin Gastroenterol Hepatol.* 2025 Nov;23(12):2328-2338.e9. Epub 2025 Apr 30

Measured Outcomes

Incremental cost-effectiveness ratio (ICER) in dollars per quality-adjusted life-year (QALY) gained

QUALY: measure the benefit of medical interventions by combining both the quantity (years of life) and quality (well-being) of life lived. One QALY equals one year in perfect health, with scores ranging from 1 (perfect health) to 0 (death)

ICER: measures the additional cost per additional unit of benefit (e.g., QALY) for one treatment or intervention over another. Lower ICERs indicate better efficiency, with decisions often guided by thresholds

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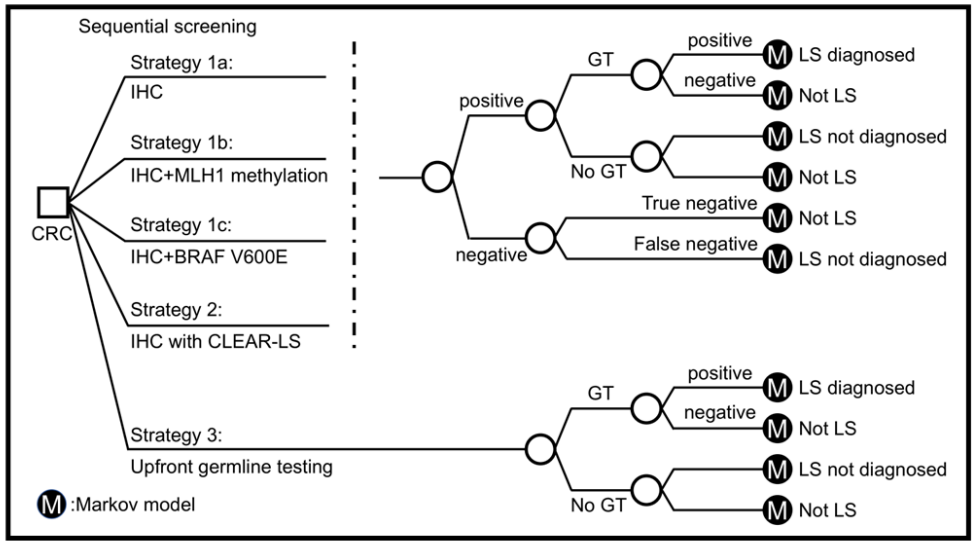
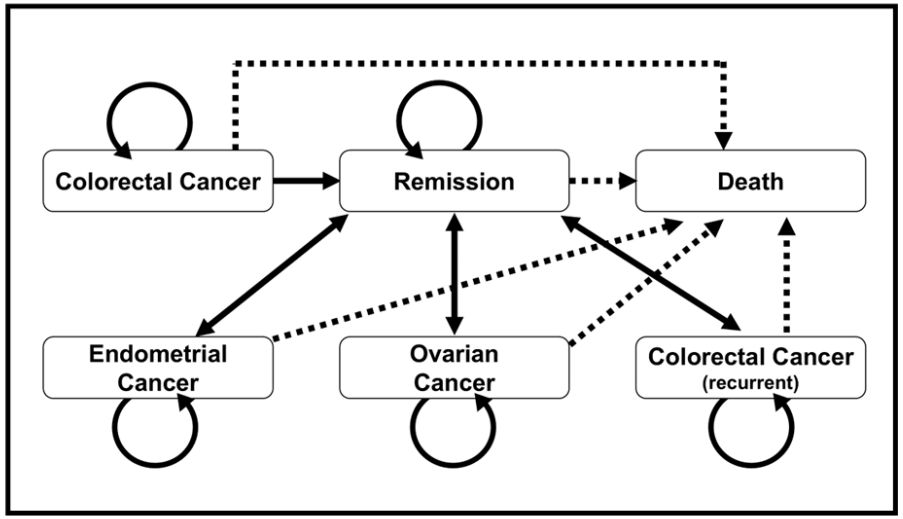
Three-step lifetime cohort simulation model

Decision tree with nested Markov cohort models

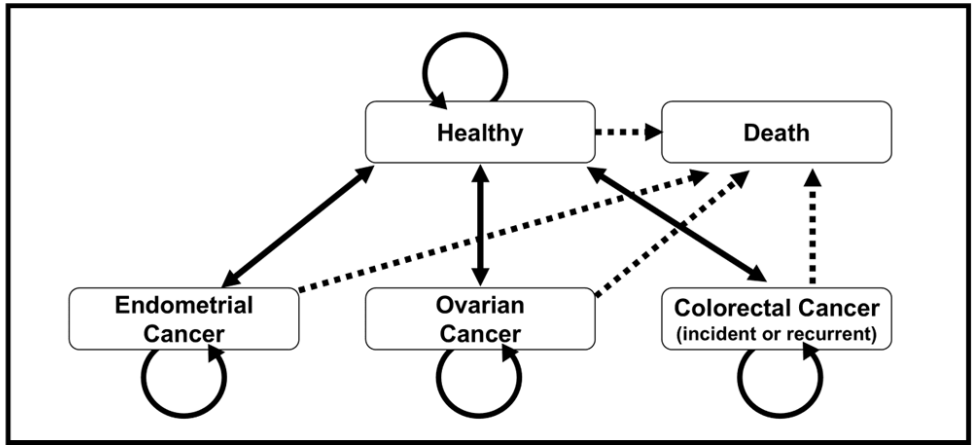
Step 1: Test characteristics (decision tree)



Step 2: Proband rest-of-life (Markov model)



Step 3: Family member cascade testing (Markov model)



Ito S & Xicola RM et al. *Clin Gastroenterol Hepatol.* 2025 Nov;23(12):2328-2338.e9. Epub 2025 Apr 30

Methods: Transition Probabilities

- Compliance rates
  - Standard care: 42%
  - CLEAR-LS intervention: 74%

- Cancer incidence and mortality
  - Prospective Lynch Syndrome Database (PLSD)
  - NCI Surveillance, Epidemiology, and End Results (SEER)

- Mortality hazard for CRC with MSI (HR=0.65)
- Incorporated the CRC risk reduction of 0.56 due to colonoscopy surveillance

Singh V et al. *J Med Genet* 2022;0:1-7
Dominguez-Valentin et al. EClinicalMedicine. 2003:58:101909.
Popat et al. J Clin Oncol. 2005;23(3):609-18.
Jarvinen et al. Gastroenterology. 2000;118(5):829-34.

Results: base case analysis (population level)

Strategy	Discounted Cost ($)	Discounted QALY	ICER ($/QALY) [95%CI]	Cost-effectiveness ratio (vs standard-of-care) ($/QALY) [95%CI]
IHC followed by germline testing (standard-of-care)	15.39 billion	1,831,000		
IHC+MLH1 methylation followed by germline testing	15.40 billion	1,831,000	Dominated	Dominated
IHC+BRAF V600 mutation followed by germline testing	15.41 billion	1,831,000	Dominated	Dominated
IHC followed by germline testing with CLEAR-LS intervention	15.45 billion	1,833,000	34,500 [28,400-44,200]	34,500 [28,400-44,200]
Upfront universal germline testing	15.65 billion	1,835,000	98,500 [73,700-216,000]	70,300 [54,600-92,500]

Colorectal cancer incidence = 153,000 incidence/year (2023)

Ito S & Xicola RM et al. *Clin Gastroenterol Hepatol.* 2025 Nov;23(12):2328-2338.e9. Epub 2025 Apr 30

Cost-effectiveness evaluation: Conclusions

1. Systems approach to improve genetic testing rates (Eg: CLEAR-LS, threshold 75%) or upfront germline testing are consistently cost-effective compared to current US clinical practice

2. Universal germline testing or interventions to reduce diagnostic attrition in the sequential testing process should be strongly considered, even in individuals >50 years of age

3. Cascade testing for relatives should be strongly encouraged

Conclusions

1. Even scientifically sound strategies can fail when they are too complex to implement effectively

2. Successful translation of medical advances requires practical interventions that address real-world barriers so all patients can benefit

3. Outcomes should be evaluated using real-world experience

4. We must continually reassess whether our strategies truly maximize patient benefit and are implemented equitably across populations

Genetic testing criteria to evaluate for Lynch syndrome

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2026
Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, Esophageal, and Gastric

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Discussion

CRITERIA FOR TESTING FOR LYNCH SYNDROME[j]

Testing is clinically indicated in the following scenarios:	
• Known LS PV in the family • Personal history of ▸ CRC, EC, or gastric adenocarcinoma (GC), or any LS-related cancer[f] diagnosed <50 y[k,l] ▸ EC ≥50 y ▸ CRC ≥50 y (category 2B) ▸ GC ≥50 y (category 2B) ▸ LS-related cancer[f] and any of the following ◊ A synchronous or metachronous LS-related cancer[f] regardless of age ◊ 1 first-degree or second-degree relative with an LS-related cancer[f] diagnosed <50 y ◊ ≥2 first-degree or second-degree relatives with an LS-related cancer[f] regardless of age • Family history[m] of any of the following[n]: ▸ ≥1 first-degree relatives with a CRC, EC, or GC diagnosed <50 y ▸ ≥1 first-degree or second-degree relatives with a synchronous or metachronous LS-related cancer[f] regardless of age ▸ ≥2 first-degree or second-degree relatives with LS-related cancers[f] including ≥1 diagnosed <50 y ▸ ≥3 first-degree or second-degree relatives with LS-related cancers[f] regardless of age • Increased model-predicted risk for LS ▸ An individual with a ≥5% risk of having an MMR gene PV based on predictive models (ie, $PREMM_5$) ◊ For individuals without a personal history of CRC and/or EC, some data have suggested using a $PREMM_5$ score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.	Strategies for Testing for LS (HRS-3)
• Personal history of CRC, EC, or any tumor with MMR deficiency determined by polymerase chain reaction (PCR), next-generation sequencing (NGS), or IHC diagnosed at any age[o,p,q] • Personal history of a P/LP variant identified on tumor somatic testing that has clinical implications if also identified in the germline[r,s]	Additional tumor-based testing (LS-A) OR Germline MGPT for LS and other hereditary cancer syndromes[t] (Strategies for Testing for LS [HRS-3])

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"It takes a village"

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Questions?

Discussion Questions

1. Were people aware of the NCCN Guideline change to recommend Multi-Gene Panel Testing for all?

   - What are you doing about this at your institution?

2. If you are in Patient Advocacy, what are you doing to make patients aware of this guideline change?

3. There are 1.5 million CRC survivors in the U.S., many who have not had multi-gene panel testing. How can we get this information out to them?

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Please take a moment to complete our survey!