HEREDITARY GI CANCER SYNDROMES:

FUTURE APPROACHES TO GENETIC DIAGNOSIS, CANCER SCREENING & PREVENTION

South Florida GI Cancer Symposium 2025

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Outline

Historic perspective and timeline

Populations of interest & potential strategies

- Individuals with Gastrointestinal Cancers
- Cancer-free, High-Risk Individuals
- General population

“Real World” considerations for Precision Public Health

Inherited Gastrointestinal Malignancies

A Historic Timeline

1895 — Family G

Dr. Aldred Warthin proposed the concept of cancer predisposition

- 4-generation pedigree of “Family G”
- Gastric, colorectal, and gynecological cancers
- Autosomal dominant inheritance

1924 — Colorectal Polyposis

Drs. Cuthbert E. Dukes & **Percy Lockhart-Mummery,** described families with Early-Onset CRC and diffuse polyposis.

- Developed the St. Mark’s Hospital Polyposis Registry in the UK

1964 — Familial Gastric Cancer & The Maori

Dr. E.G Jones identified “Family A” of Māori ethnicity in New Zealand with a high burden of gastric cancer

- Highly penetrant, aggressive form of diffuse-type gastric cancer
- 1/3 of the family affected with gastric cancer

1966 — Cancer Family Syndrome

Dr. Henry Lynch reported on a family history with Early-Onset CRC and a non-polyposis phenotype

- Noted similarities to Family G
- Renamed condition to ”Hereditary Non-Polyposis Colorectal Cancer”

1994 — Familial Pancreatic Cancer

Familial Pancreatic Cancer was defined in 1999

- Collaborative efforts of The National Familial Pancreas Tumor Registry, established in 1994
- **Dr. Gloria Petersen** led the Pancreatic Cancer Genetic Epidemiology Consortium (PACGEGE) which was organized in 2002

Molecular Basis of Inherited GI Cancers

Major advances in gene discovery in the late 20th century

- *1991, APC* in Familial Adenomatous Polyposis (FAP)
- 1993-1994, Lynch syndrome mismatch repair genes (*MSH2, MLH1, PMS2, MSH6)*
- 1997, *PTEN* in Hamartoma Tumor Syndrome
- 1998, *STK11* in Peutz-Jeghers Syndrome
- 1999, *E-cadherin* in Hereditary Diffuse Gastric Cancer (HDGC)
- 2002, *MUTYH,* in attenuated/classic polyposis (MAP)

1993, Microsatellite Instability discovered as a “unique pathway” through which CRC could evolve

Benefits of Identifying Germline Cancer Predisposition

- Therapeutic and surgical decision-making
- Surveillance following treatment of primary cancer
- Surveillance for associated cancers/ risk-reducing surgeries
- Screening and genetic testing of families
- Reproductive counseling: preimplantation genetic diagnosis
- Chemoprevention
- Immunoprevention and vaccines

Genetic Diagnosis of Inherited GI Cancer Syndromes in ***Cancer Patients***

Which patients with GI malignancies undergo germline genetic testing?

- CRC <50 years
- Pancreatic cancer
  - FDRs of individuals with Pancreatic cancer
- Personal history of multiple cancers
- Personal history of >10 adenomas
- Family history of multiple GI cancers
- Abnormal tumor testing

  MSI-High and/or abnormal IHC testing

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

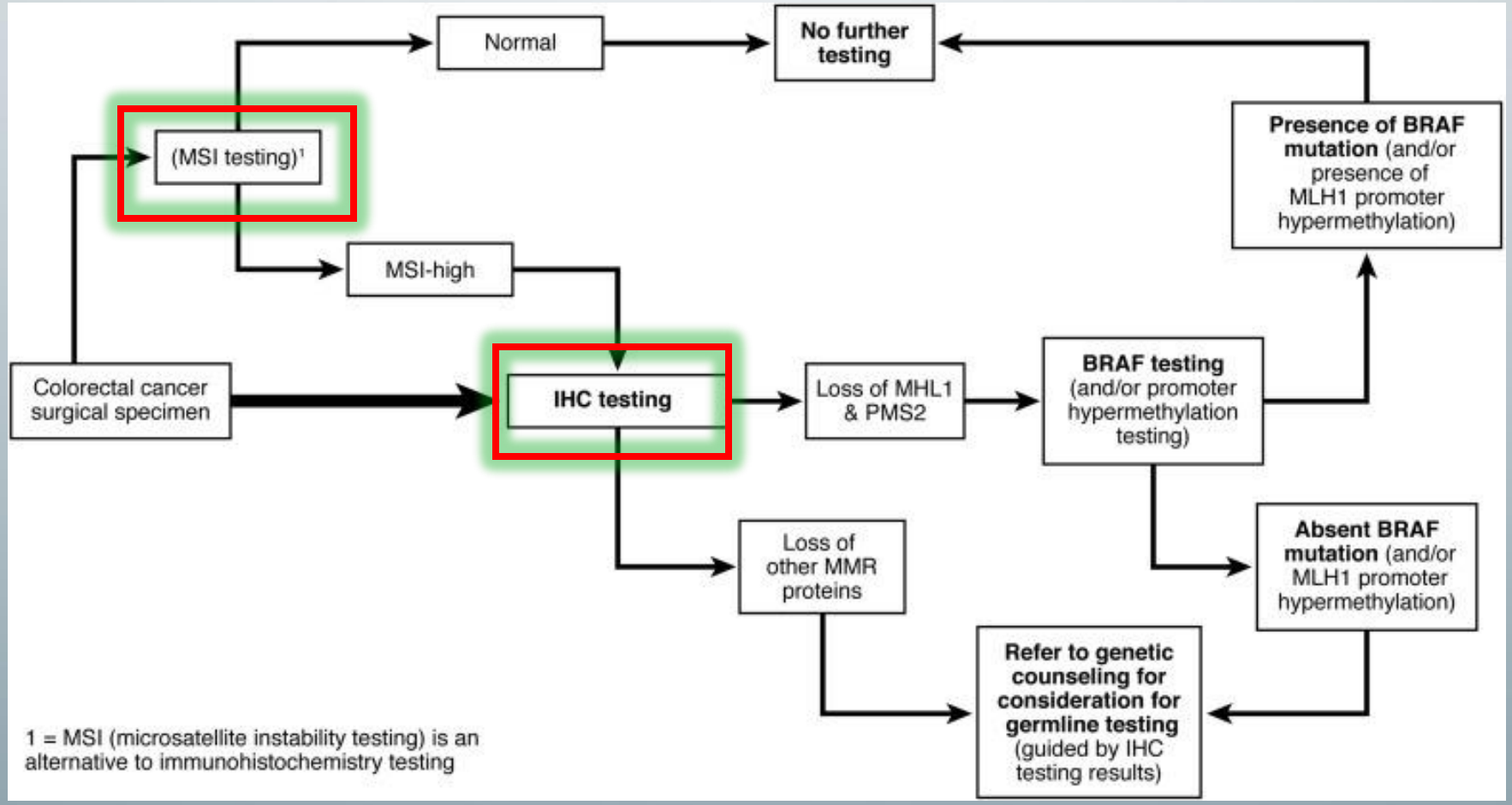
  Universal screening of all CRC and EC tumors for MMR deficiency

- **Genotype variation in cancer risk**

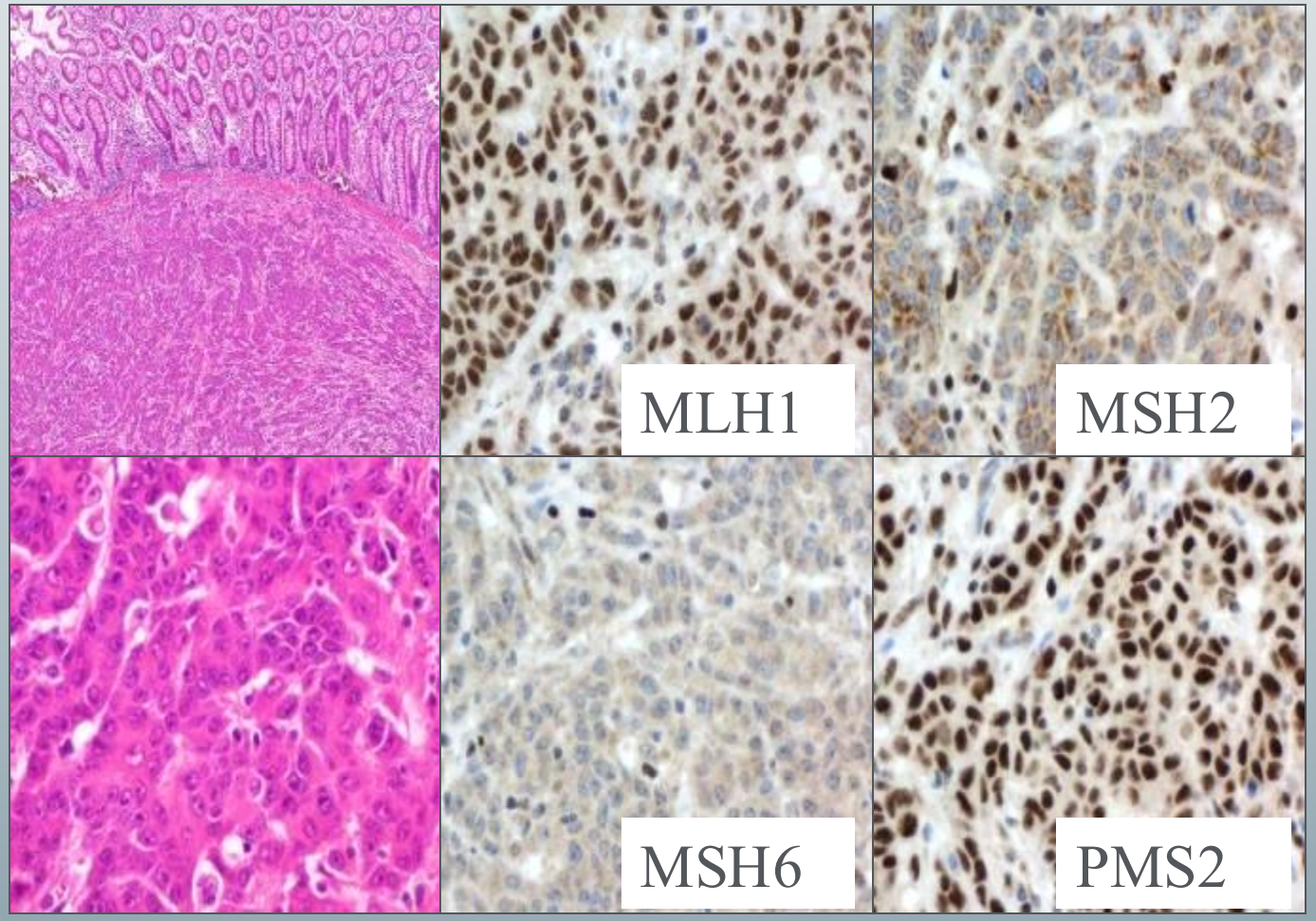
  MLH1 and *MSH2*: strong penetrance/high cancer risks; less prevalent

  MSH6 and *PMS2*: weak penetrance/low cancer risks; most prevalent

UNIVERSAL TUMOR TESTING OF CRC FOR LYNCH SYNDROME



UNIVERSAL TUMOR TESTING OF CRC FOR LYNCH SYNDROME



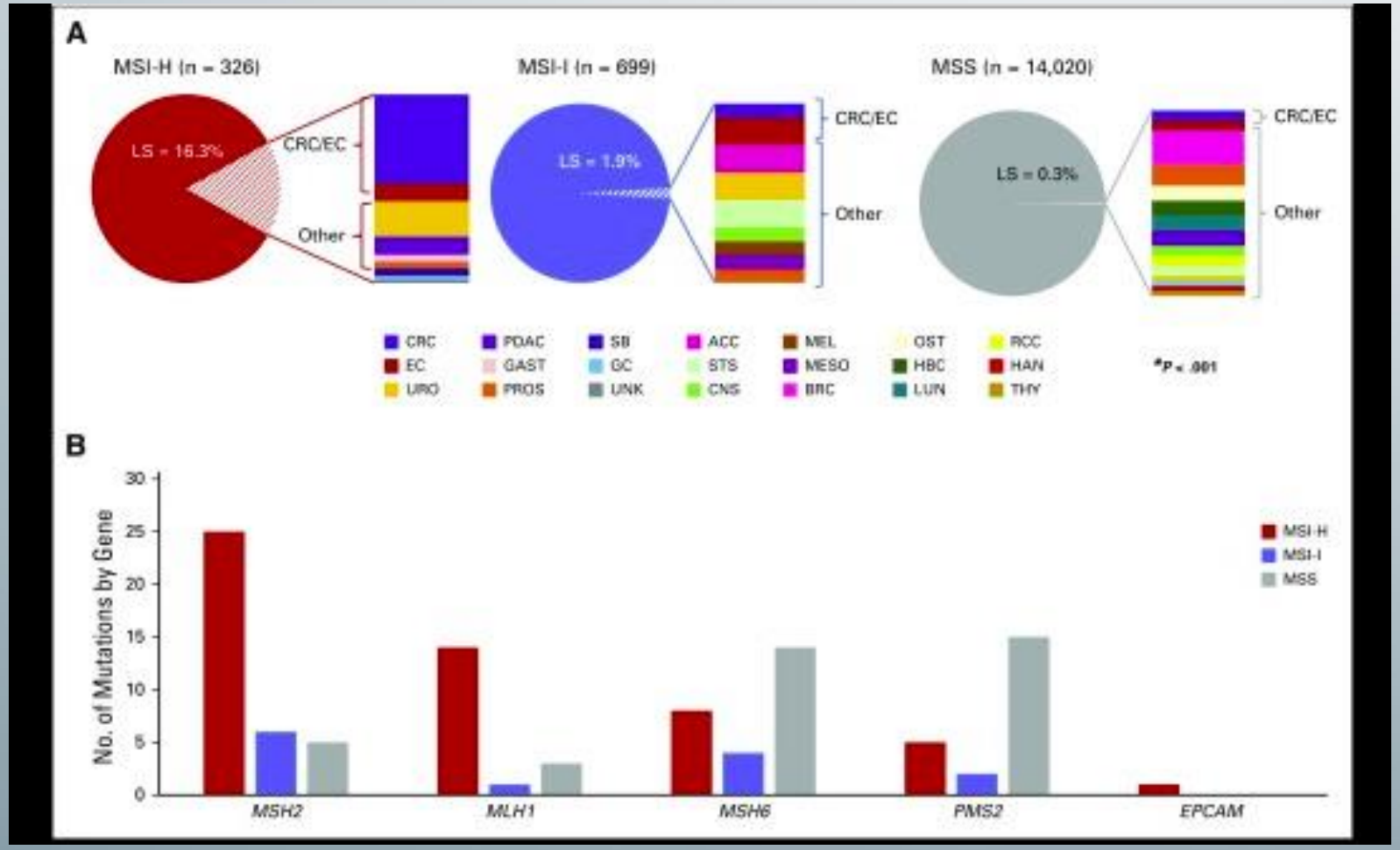
Immunohistochemistry with loss of MSH2/MSH6 expression= MMRd

MSI Testing Beyond CRC

- MSI testing is a strong predictive biomarker for response to immune checkpoint therapy, regardless of primary site
- Supports MSI testing for any advanced solid tumor
- Single-site study reported prevalence of Lynch syndrome across solid tumors according to MSI status
  - Over 15,000 subjects with >50 different types of primary cancer
  - Well-annotated tumor and matched normal DNA sequencing results, including paired germline MMR gene testing

Latham A et al. JCO 2019

PREVALENCE OF LYNCH SYNDROME ACROSS SOLID TUMORS



- MSI-H is predictive of Lynch syndrome across a broad tumor spectrum
- *Germline testing for all patients with an MSI-H tumor regardless of cancer type or family cancer history*
- Important to consider use of *parallel* tumor profiling and germline testing

Latham A et al. JCO 2019
Yurgelun M, Kastrinos F. JCO 2019

Therapeutic Decision-Making Directs Genetic Diagnosis of Inherited GI Cancer Syndromes

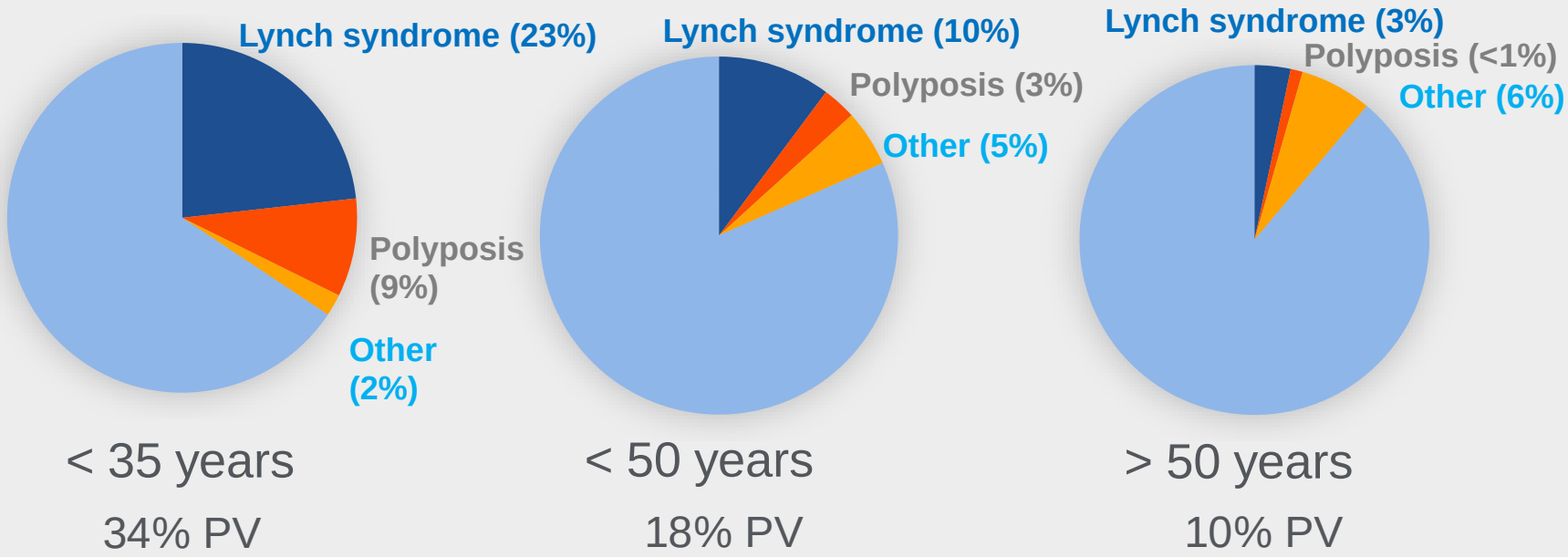
- Cancer treatment often directed by:
  Tumor testing with MSI/sequencing
  - Multi-Gene Panel Testing (MGPT)

- Treatment was directed by *Universal Germline Multi-Gene Panel Testing* results in 30% of patients with solid tumors

- MGPT has transformed genetic risk assessment

Samadder NJ, et al. *JAMA Oncol*. 2021

Outcomes of Multi-Gene Panel Testing in CRC



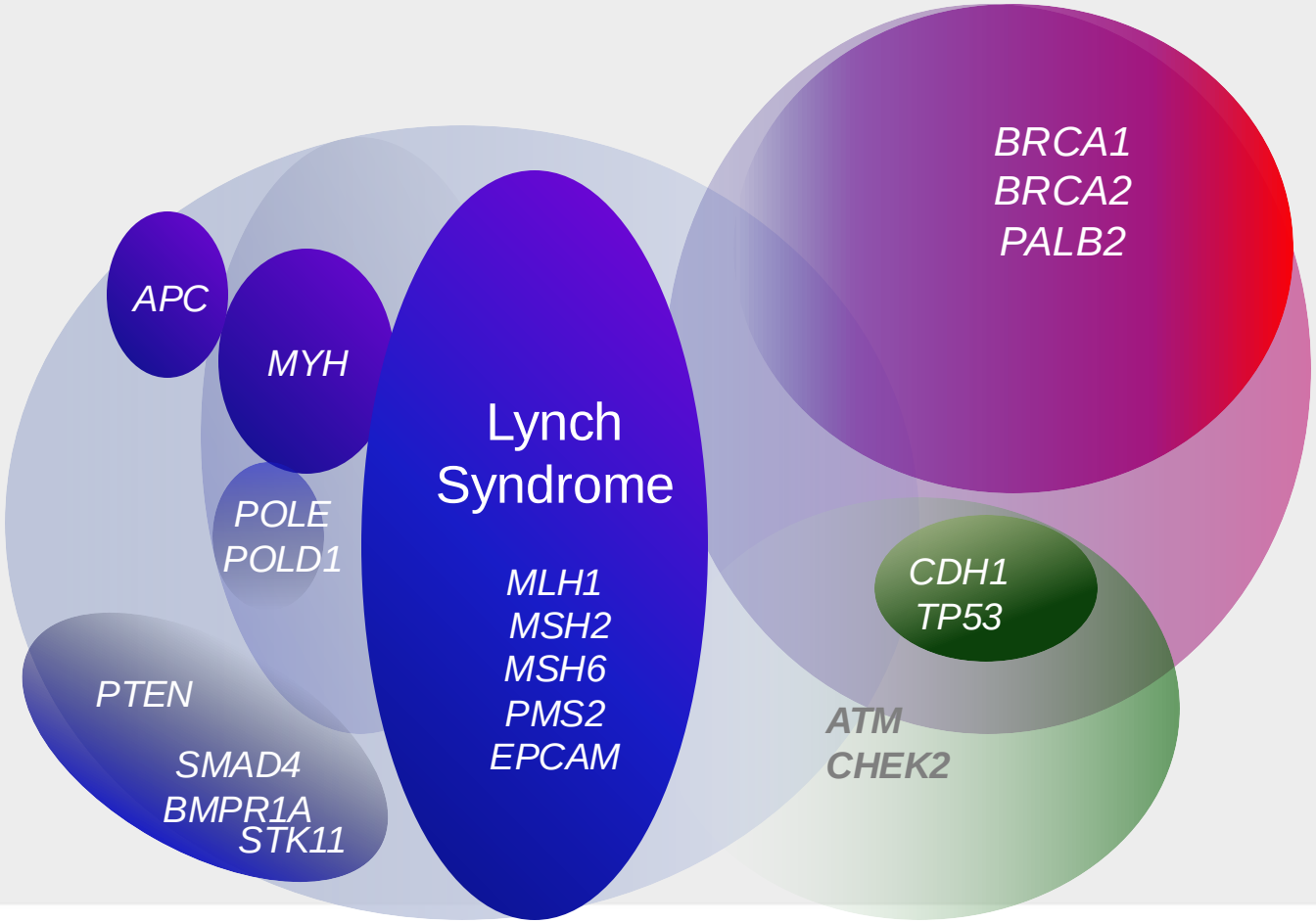
Other pathogenic variants	
High penetrance	Moderate penetrance
BRCA1	*CHEK2*
BRCA2	*ATM*
TP53	
CDKN2A	
PALB2	

Current guidelines to screen with Universal Tumor Testing

- Miss 34% of carriers with pathogenic variants
- Miss 7% of Lynch syndrome carriers

Stoffel E, et al. *Gastroenterology.* 2020
Pearlman R, et al. *JCO Precis Oncol*. 2021

Pathogenic Variants associated with CRC



Future Consideration: Upfront Multi-Gene Panel Testing in *all* CRC

- Optimal approach to the identification of Lynch syndrome
- Includes pathogenic variants in other highly penetrant, actionable, genes
- Potential opportunity to readily identify carriers from under-represented populations
  - Variable universal tumor screening for Lynch syndrome in non-white CRC patients*

*Muller, *Clin Gastroenterol Hepatol*. 2018

Challenges and Opportunities

Challenges

- Detection of moderate-penetrance genes
  - Risk estimates and management unclear
- Detection of Variants of Uncertain Significance (VUS)

Opportunities

- Lessons learned from Universal Germline Screening in Pancreatic Cancer
  - NCCN recommends testing all PDAC patients and/or first-degree relatives
  - Address point-of care testing, disclosure of results, post-test counseling, cascade testing of relatives

Inherited Cancer Predisposition and Upper Gastrointestinal Tract Cancers

Recommendations limit testing to genes related to Inherited GI Cancer syndromes

- *Gastric cancer*: Hereditary Diffuse Gastric Cancer, Polyposis, Lynch syndrome
- *Small bowel cancer*: Polyposis syndromes, Lynch syndrome
- *Esophageal cancer*: None (investigational)

~5-10% are associated with a pathogenic germline variant

Genetic Diagnosis of Inherited GI Cancer Syndromes in ***Cancer free, High-Risk Individuals***

Seeking the Previvors

Previvors

- Individuals *without cancer* who carry a germline pathogenic variant; inherited risk of cancer

Current Strategies to identify Previvors

- Cascade Testing when a familial pathogenic variant is known
- Risk assessment based on family cancer history
  - Clinical prediction models, ie. PREMM; EMR-based family history tools

PREMM5 MODEL | LYNCH SYNDROME

Lynch syndrome prediction model

MLH1, MSH2, MSH6, PMS2, and *EPCAM* gene mutations

- Estimates the cumulative probability an individual carries a MMR gene

  Logistic regression analysis

- Proband + Family Cancer History

- Inclusion in NCCN Guidelines since 2014

http://www.premm.dfci.harvard.edu

Kastrinos et al. *JCO*; 2017

1 Patient information

Sex

- Male
- Female

Current age (years)

42

Has the patient had colorectal cancer?

- No
- Yes

If so, how many separate colorectal cancers?

- One
- Two or more

If one, what was the age at diagnosis? (If unknown, please estimate)

37

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 family*

How many first-degree relatives have had colorectal cancer?

- None
- One
- Two or more

If more than one, what was the youngest age at diagnosis? (If unknown, please estimate)

49

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

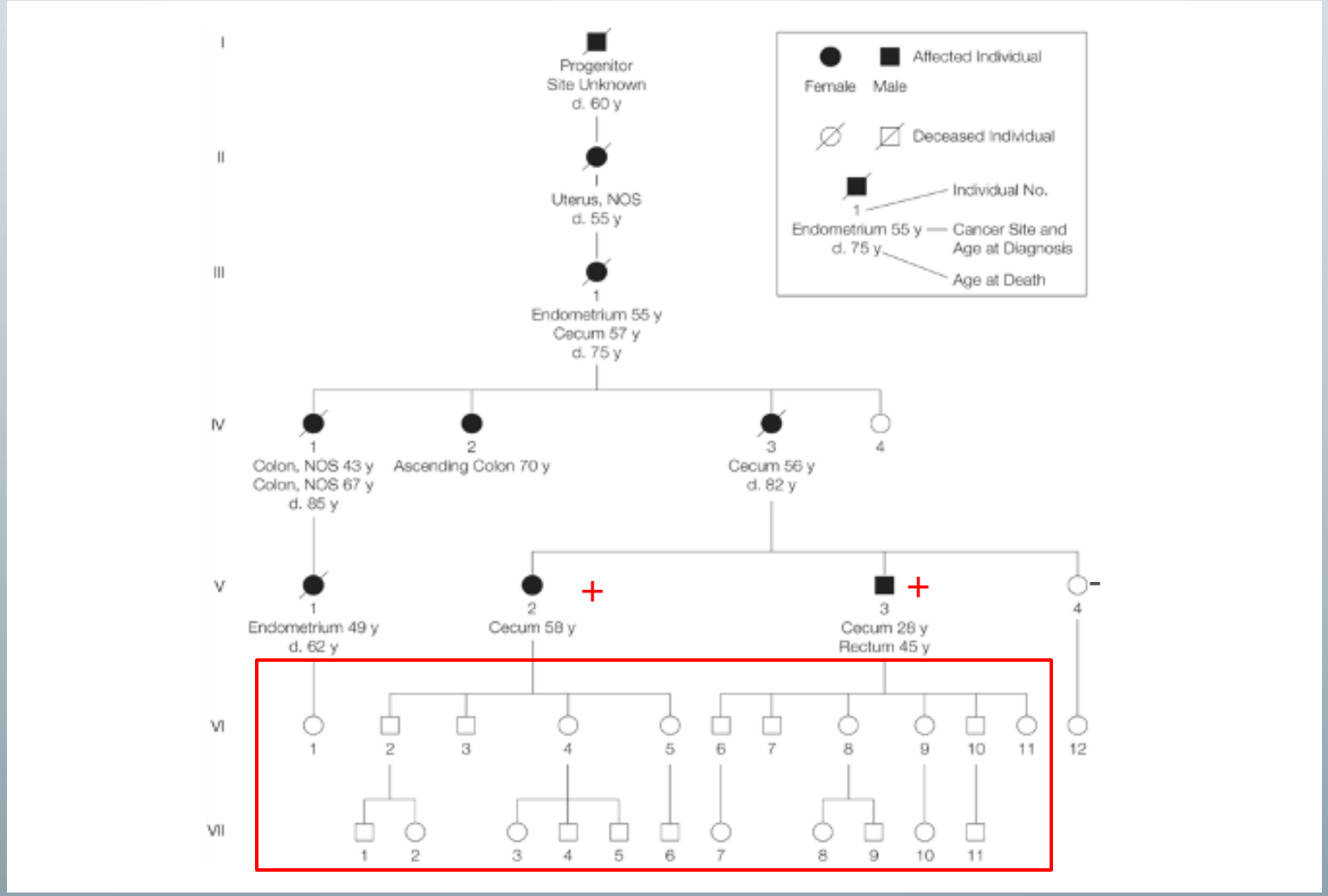
Overall predicted probability of *MLH1, MSH2, MSH6, PMS2,* or *EPCAM* mutation

1.7%

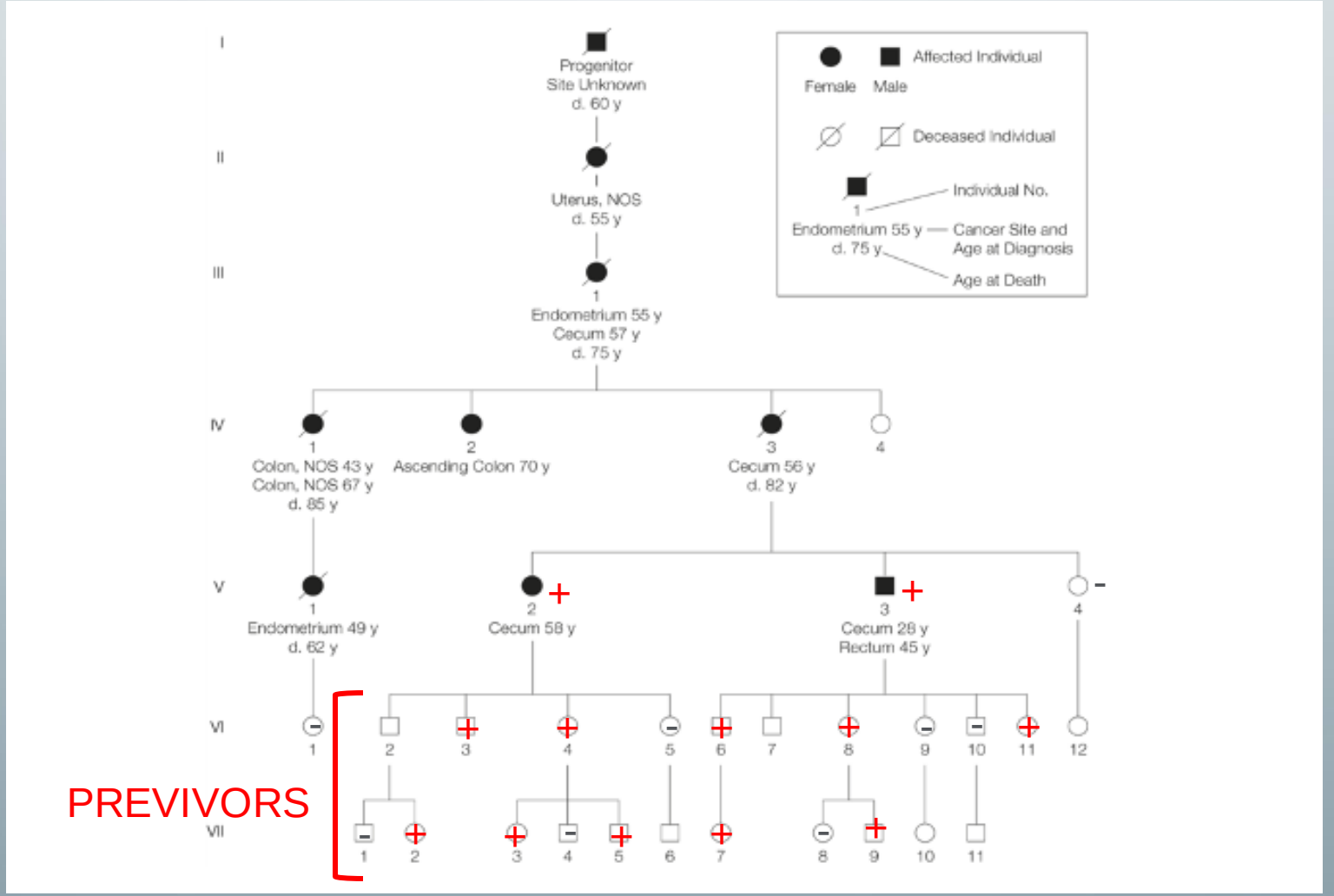
If the overall predicted probability is ≥ 2.5%

Referral for genetic evaluation is recommended. This may include tumor sample microsatellite instability (MSI) or immunohistochemistry (IHC) testing, genetic counseling, and/or germline genetic testing. (Kastrinos F. et al. Development and validation of the PREMM5 model for comprehensive risk assessment of Lynch syndrome. Journal of Clinical Oncology. 2017 May 10. Advance online publication. DOI: 10.1200/JCO.2016.69.6120. $PREMM_5$ JCO)

CASCADE TESTING: SEEKING THE PREVIVORS



THE IMPACT OF CASCADE TESTING



Barriers in Identifying Previvors

Low Uptake of Cascade testing

- Uptake ~20-40%
- Relies on family communication & risk perception
- Limited access to genetic counseling
- Current delivery model may be a limiting factor
  - For a newly identified carrier with cancer, GC recommends cascade testing
  - Too few opportunities of providers to address cascade testing

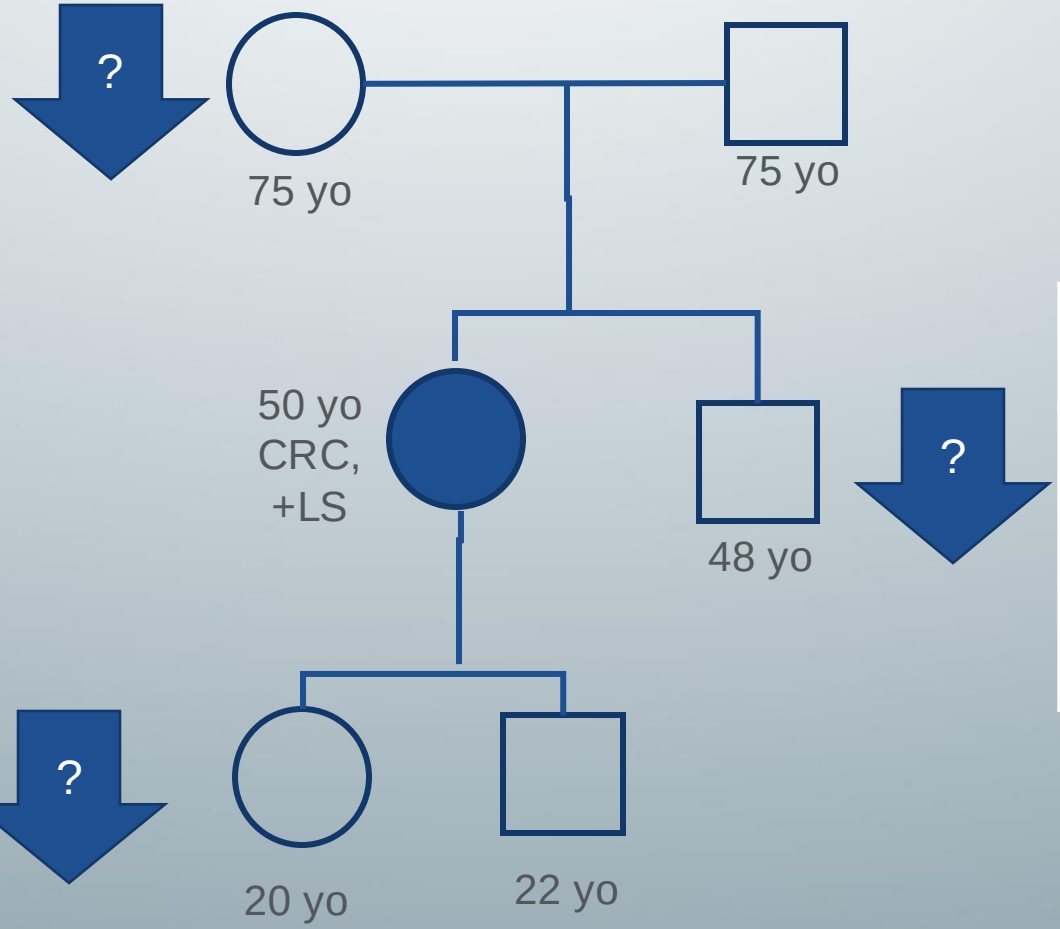
Cascade Testing: A Call to Action

Identified +carriers undergo frequent endoscopy/colonoscopy

- Gastroenterologists often interface annually, ie. Lynch syndrome, polyposis, eligible for PDAC surveillance
- An *opportunity to engage* in dialogue about cascade testing

IMPACT OF CASCADE TESTING ON FDR CRC RISK

Strategy	% Develop Cancer	%Cancer Death
No cascade testing	4.26%	1.49%
Cascade testing	2.47%	0.52%
Testing Benefit	-1.79% Develop Cancer	-0.97% Cancer Deaths

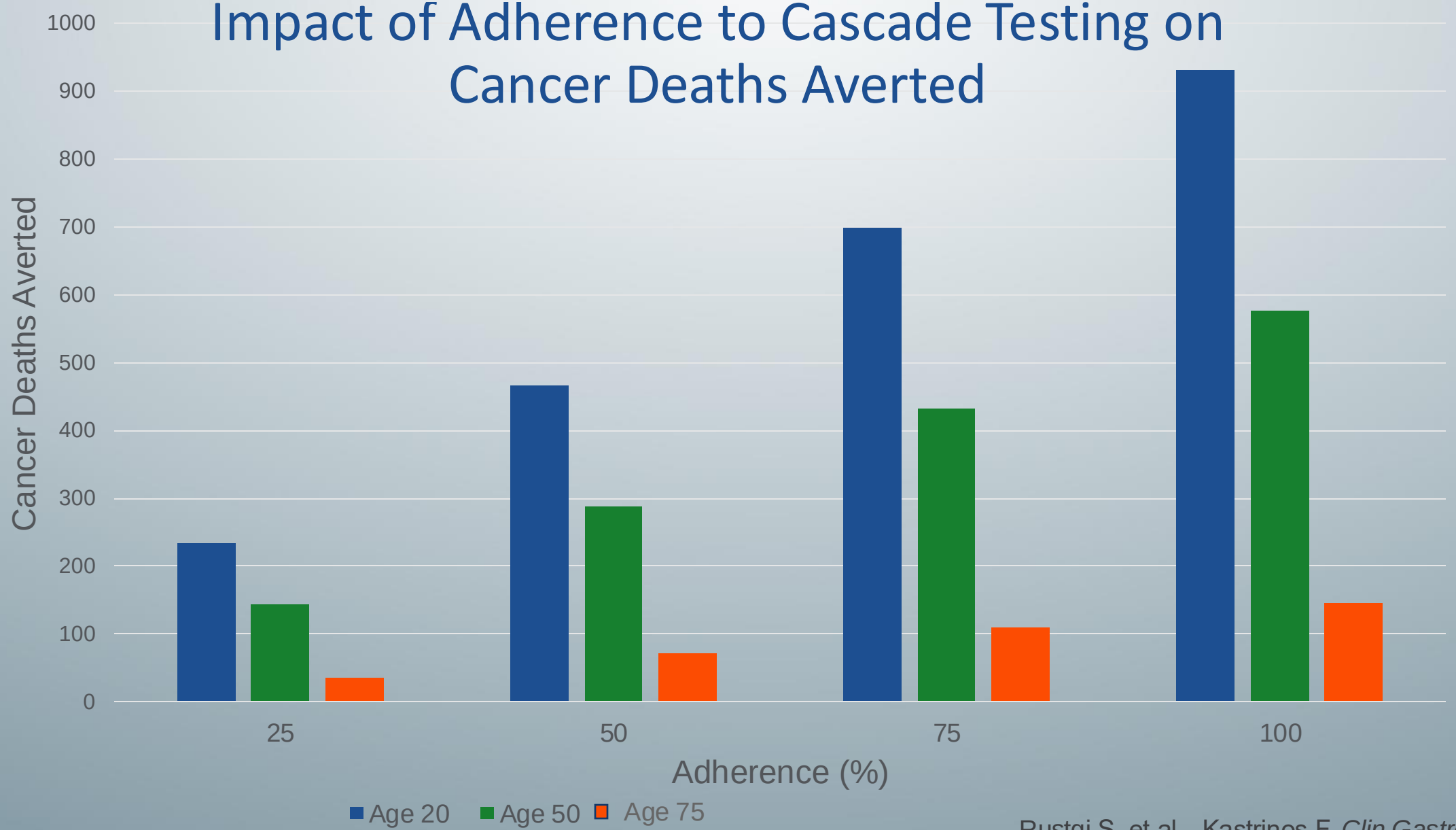


Strategy	% Develop Cancer	%Cancer Death
No cascade testing	15.86%	5.17%
Cascade testing	6.63%	1.34%
Testing Benefit	-9.23% Develop Cancer	-3.83% Cancer Deaths

Strategy	% Develop Cancer	%Cancer Death
No cascade testing	26.13%	7.75%
Cascade testing	9.67%	1.55%
Testing Benefit	-16.46 % Develop Cancer	-6.2% Cancer Deaths

Rustgi S, et al…Kastrinos F. *Clin Gastro Hep* 2025

Impact of Adherence to Cascade Testing on Cancer Deaths Averted



Rustgi S, et al…Kastrinos F. *Clin Gastro Hep* 2025

Gastroenterologists: A Call to Action

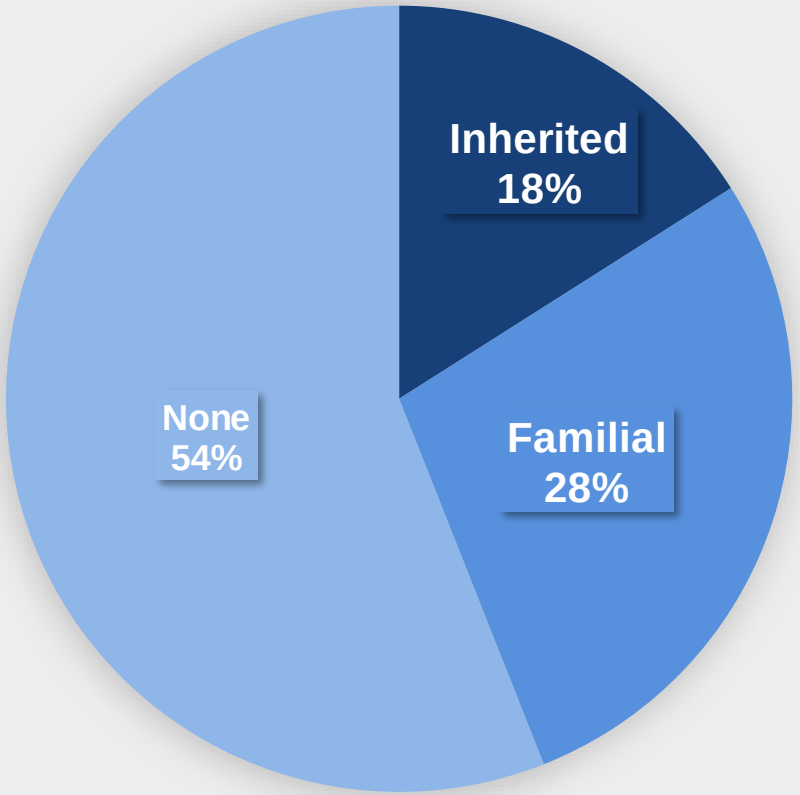
Identified +carriers undergo frequent endoscopy/colonoscopy

- Gastroenterologists often interface annually, ie. Lynch syndrome, polyposis, eligible for PDAC surveillance
- An *opportunity to engage* in dialogue about cascade testing

Consider expanding our endoscopic reports' Recommendation section

- Include recommendations to family members
- Leverage endoscopy reporting systems to include templates/verbiage for:
  - Cascade testing in at-risk relatives of + carriers
  - Colonoscopy recommendation with start age for FDRs of patients with CRC, advanced adenomas

Nearly half of all Early Onset CRC is Inherited/Familial: POTENTIAL FOR PREVENTION



INHERITED

- Genetic testing in all cases of EO-CRC
- Promote Cascade testing
  - Initiate early initiation of colonoscopy

FAMILIAL

- Expand recommendations for screening to family members
- Screening start at 40 years (or earlier) for FDRs of CRC and advanced adenomas

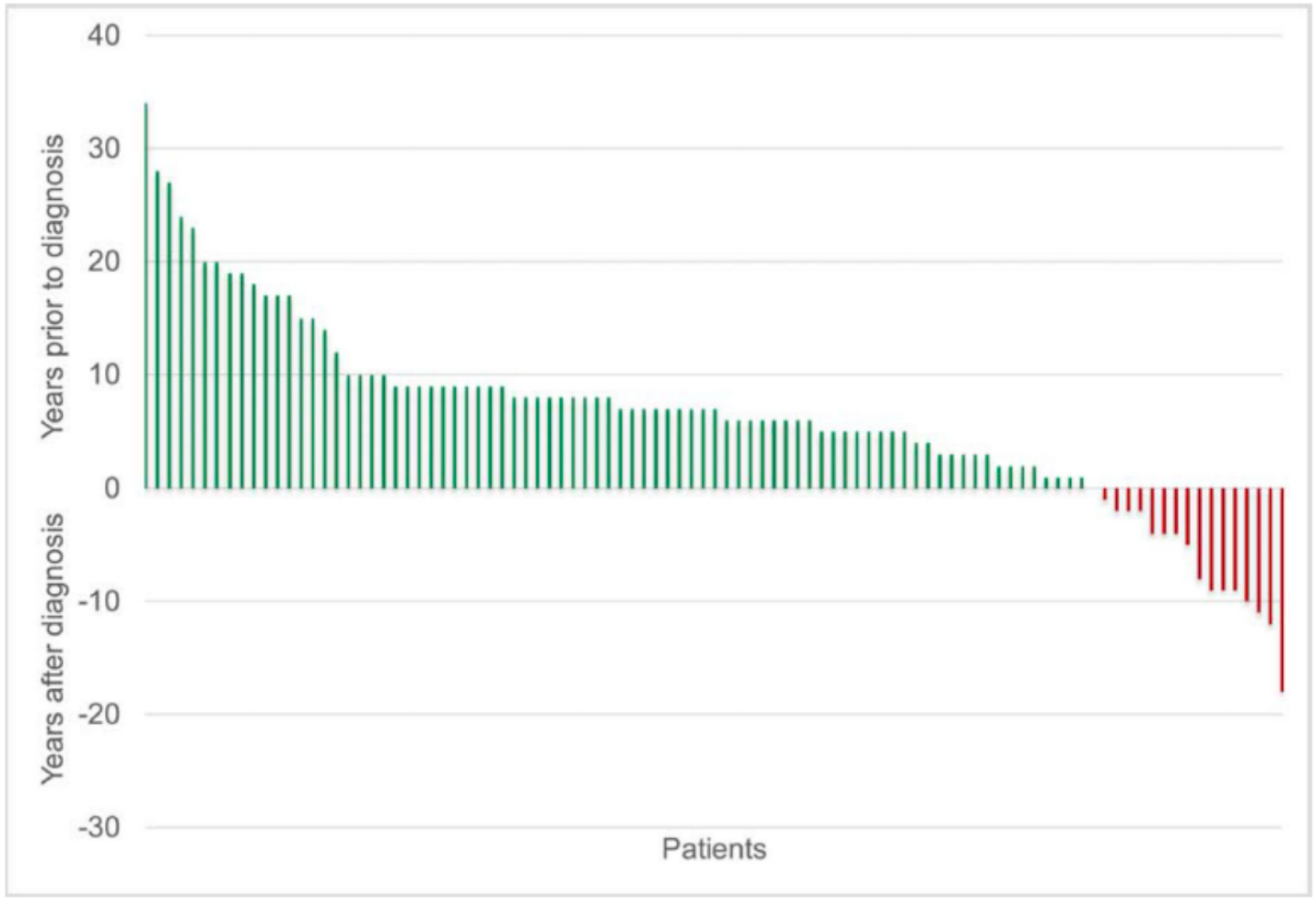


Figure 1.
Waterfall plot presenting the difference between age of colorectal cancer onset and recommended age to initiate colorectal cancer screening based on family history of a first-degree relative with colorectal cancer. Each bar represents a single patient, with green representing those who would have started screening prior to their diagnosis and red those who would have started screening after diagnosis.

EO-CRC cases with family history

- 82.5% of cases could have been down-staged
- 67% prevented if appropriate recommendations were made

Stanich P, et al. *Gastroenterology* 2021

Identified Previvors Benefit from Risk-Reducing Strategies

- Risk-reducing surgeries
- Other, non-GI screening
- Chemoprevention
- *Opportunity to assess modifiable risk factors in identified +carriers*
  - Lifetime risk of gastric cancer in +Carriers with +*HPylori* vs non-carriers:
    - 45.5% vs. 14.4%*
  - Associated genes: *APC, CDH1, MLH1, MSH2, MSH6, PMS2, ATM, BRCA1, BRCA2*

*Usui Y, et al. *NEJM*, 2023

Chemoprevention & Immunoprevention in Lynch syndrome

- Chemoprevention for CRC
  - ASA use and the CAPPS2 study
- Immunoprevention of Lynch syndrome tumors
  - Vaccines can generate immune-mediated response against the tumor associated antigens specific to Lynch Syndrome tumors and premalignant lesions
  - Lynch syndrome specific vaccines may prevent lesion formation, progression, or lead to regression

Genetic Diagnosis of Inherited GI Cancer Syndromes in the ***General Population***

Population-based Germline Screening for Precision Public Health

- CDC's Office of Public Health Genomics (OPHG) classifies medical conditions eligible for genomic evaluation in Tiers

- TIER 1 applications:
  - *"Significant potential for positive impact on public health"*
  - *"At present, these conditions are poorly ascertained by the healthcare system that many individuals and families affected by them are not aware that they are at risk"*

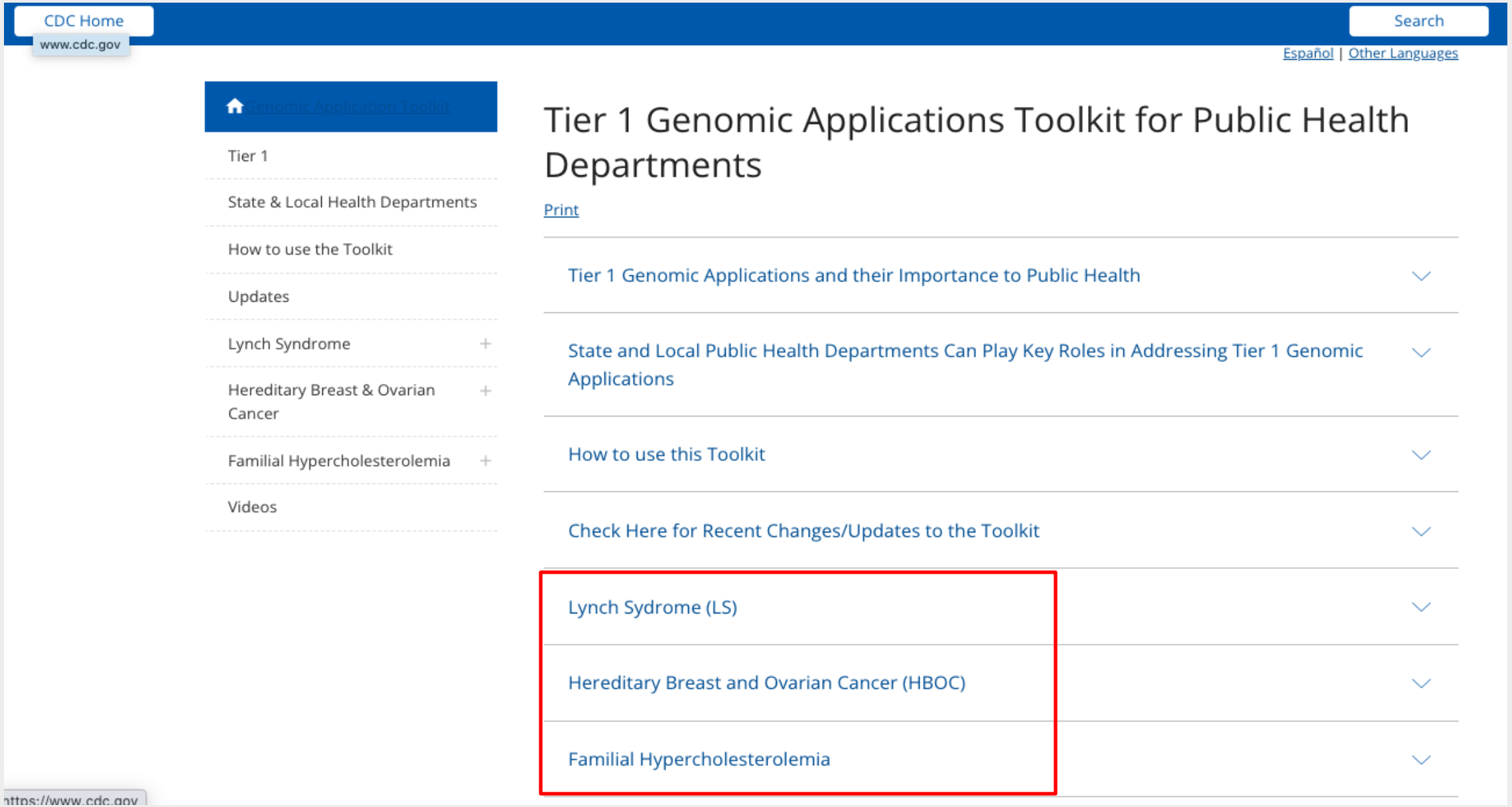
- Population-based germline testing can serve as a potential risk assessment tool for *common genetic conditions with high penetrance*

CDC's Tier 1 Genomic Applications

(1) Lynch syndrome

(2) Hereditary Breast Ovarian Cancer Syndrome

(3) Familial Hypercholesterolemia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Videos
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Print
Tier 1 Genomic Applications and their Importance to Public Health
State and Local Public Health Departments Can Play Key Roles in Addressing Tier 1 Genomic Applications
How to use this Toolkit
Check Here for Recent Changes/Updates to the Toolkit
Lynch Sydrome (LS)
Hereditary Breast and Ovarian Cancer (HBOC)
Familial Hypercholesterolemia

Population-based screening for Lynch Syndrome

The TAPESTRY trial

- Prospective study of 100,000 individuals who undergo WES within an integrated health system
- Feasibility Study : To assess prevalence of CDC's Tier 1 cancer syndromes

Results

- 44,306 tested; 550 gene + carriers identified (1.3%)
- 387 (0.9%) with HBOC; 163 (0.4%) with Lynch syndrome
- 39.2% missed by NCCN criteria
  - 49% of carriers from racial/ethnic minority groups missed
- Reasons NCCN criteria unmet: no personal history of cancer, insufficient number of relatives with cancer, patient's cancer type was not related to Lynch or HBOC

Samadder, AACR 2023

All of Us Research Initiative: Population-based screening for Lynch Syndrome

The *All of Us* Research Initiative

- Population-based US cohort study to advance precision medicine with of 1 Million participants
- Evaluated prevalence and clinical features of Lynch syndrome
  - Provides novel data compared to existing studies of European populations, most often limited to family cancer registry data, not representative of diverse populations

Results

- Prevalence of Lynch Syndome in the US population: 1 in 354 individuals
- Higher prevalence of PMS2 and MSH6 pathogenic gene variants compared MLH1 and MSH2
- Up to 63.2% of carriers lacked personal or family cancer history
  - Diagnosis of LS may have potentially been missed

Findings support population-based germline genetic testing as a potential strategy to identify individuals with LS, particularly those unaffected by cancer

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

Population Screening and "Real World" Considerations

Considerations to *effectively screen* the general population for Lynch syndrome

- A significant portion of identified +carriers need to act on recommendations
- Assess availability of resources
  - Caution about use of resource-intensive interventions in under-resourced health systems
  - Consider multimodal-screening strategies with potential integration of non-invasive options with endoscopy
- Methods do not exacerbate health inequities
  - Health equity in genomic and precision medicine; navigator programs

Take Home Messages: Hereditary GI Cancers & Genetic Risk Assessment

Cancer patients will be better identified due to decision-making for targeted therapies

- CRC: need for consensus on Universal Germline testing and update guidelines
- PDAC: optimize the point-of-care approach
- Upper GI Cancers: quantify risks by genotype, develop guidelines

Cancer-free individuals at high-risk

- Provider recommendations & guidelines for cascade testing in at-risk relatives

General population

- Ongoing studies from integrative health systems will report results
- Continued research and collaborations

Thank you

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