Germline Testing for Colorectal Cancer – When is it necessary?

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Disclosures

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Germline Testing for Colorectal Cancer – When is it necessary?

Hereditary colorectal cancer syndromes

Who should have germline testing for a hereditary colorectal cancer syndrome

Yield of germline testing in colorectal cancer

Pros and cons of universal germline testing for colorectal cancer

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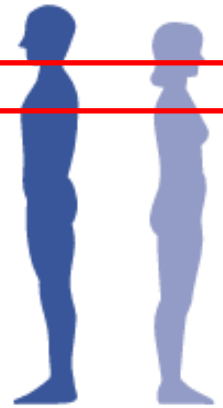
Colon cancer is common

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2022 Estimates

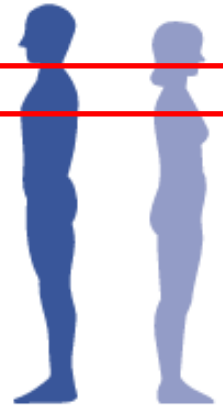
Estimated New Cases

Male			Female		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All sites	**983,160**		**All sites**	**934,870**	



Estimated Deaths

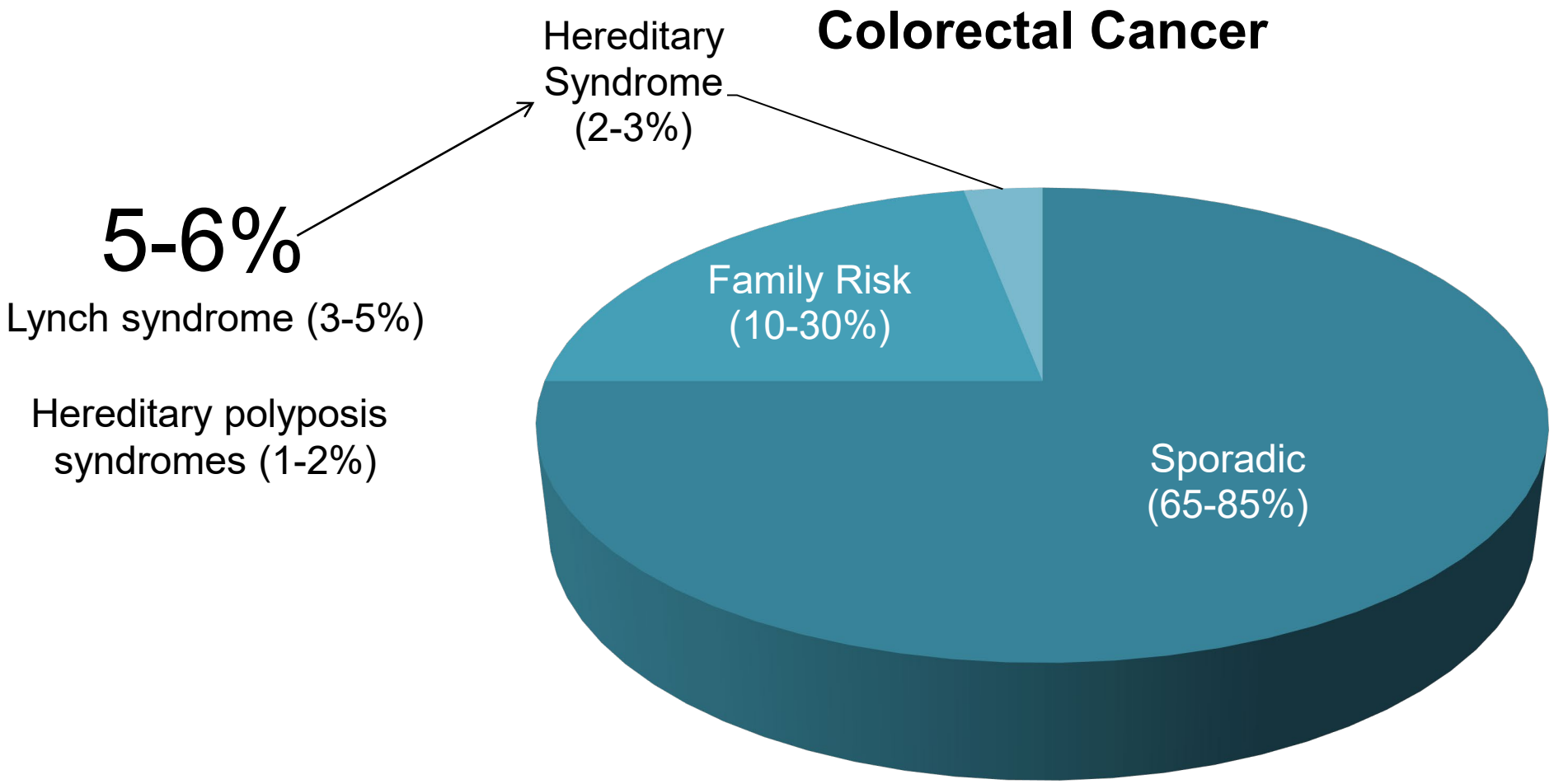
Male			Female		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All sites	**322,090**		**All sites**	**287,270**	



~4-5% lifetime risk of developing colon cancer

ACS, Cancer Facts and Figures, 2022

Familial and genetic risk for colorectal cancer



Adapted from Burt et. al., *Gastroenterology*, 2000

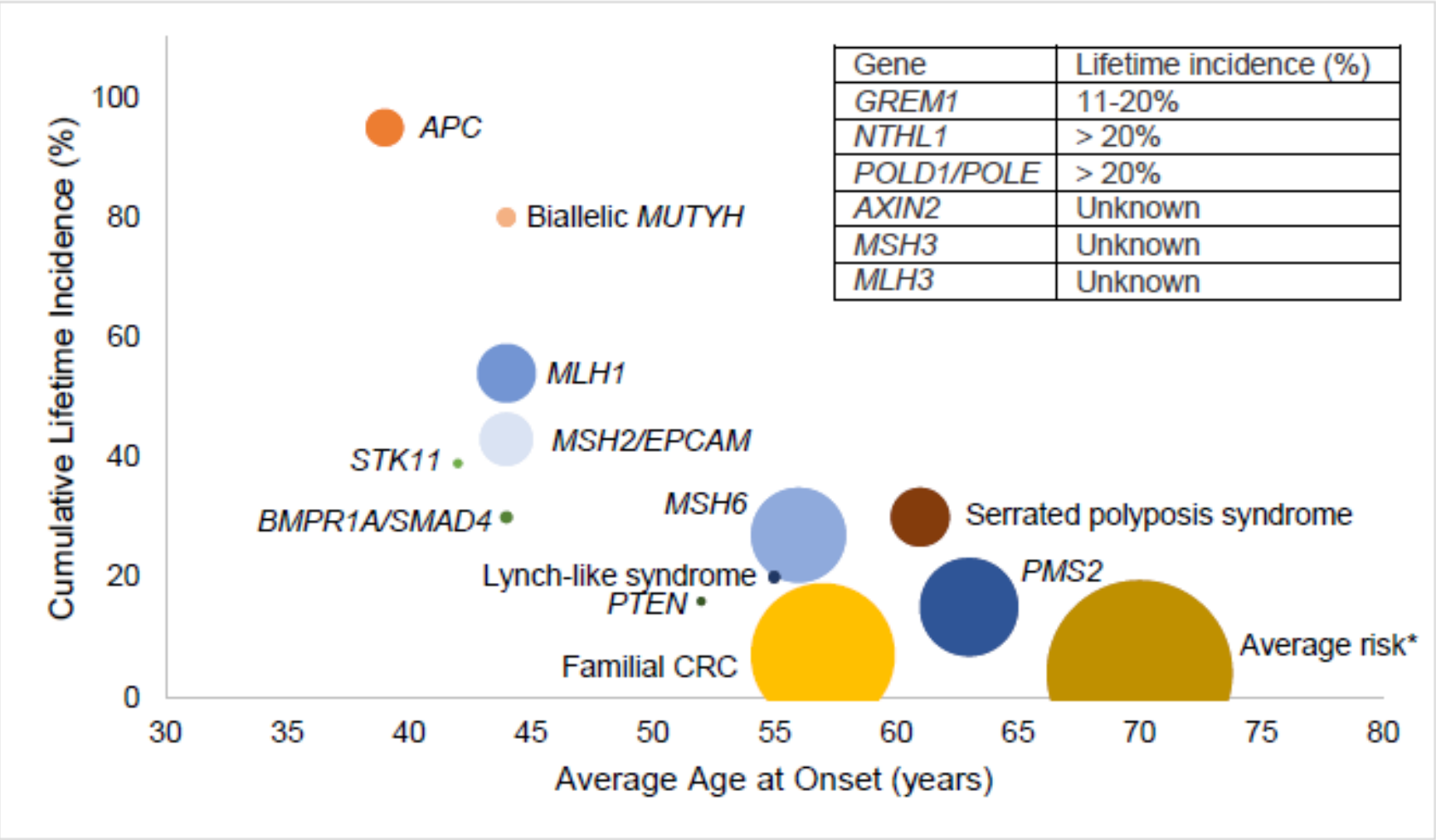
Hereditary colorectal cancer risk syndromes

Gene(s)	Inheritance	Syndrome(s)	Polyp type(s)
Historically well-established syndromes			
APC	AD	Familial adenomatous polyposis (FAP) or attenuated FAP (AFAP)	Adenoma
MLH1, MSH2, MSH6, PMS2, EPCAM	AD	Lynch syndrome (LS)	Adenoma
MUTYH (biallelic)	AR	*MUTYH*-associated polyposis (MAP)	Adenoma, sessile serrated
PTEN	AD	*PTEN* hamartoma tumor syndrome (PHTS), Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome	Hamartoma, adenoma, inflammatory, hyperplastic, ganglioneuroma, intramucosal lipoma
SMAD4, BMPR1A	AD	Juvenile polyposis syndrome (JPS)	Hamartoma (juvenile type)
STK11	AD	Peutz-Jeghers syndrome (PJS)	Hamartoma (Peutz-Jeghers type)
Newer syndromes			
AXIN2	AD	*AXIN2*-associated polyposis	Adenoma
GREM1	AD	Hereditary mixed polyposis syndrome (HMPS)	Adenoma, hyperplastic, hamartomas, inflammatory, and polyps of mixed subtype
MSH3	AR	*MSH3*-associated polyposis	Adenoma
NTHL1	AR	*NTHL1*-associated polyposis	Adenoma
POLD1, POLE	AD	Polymerase proofreading-associated polyposis (PPAP)	Adenoma
RNF43	AD	*RNF43*-associated serrated polyposis syndrome	Sessile serrated, traditional serrated adenoma, hyperplastic
Emerging evidence genes			
RPS20, GALNT12, MLH3			

AD - autosomal dominant, AR - autosomal recessive

Long J.M…Katona B.W., *Curr Treat Options Gastro*, 2021

Hereditary colorectal cancer risk syndromes



Gene	Lifetime incidence (%)
GREM1	11-20%
NTHL1	> 20%
POLD1/POLE	> 20%
AXIN2	Unknown
MSH3	Unknown
MLH3	Unknown

Figure 1: Lifetime incidence and average age of onset of colorectal cancer by gene or syndrome

Foda Z., Dharwadkar P., Katona B.W., *Best Pract Res Clin Gastroenterol*, 2023

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Pros and cons of universal germline testing for colorectal cancer

When to test for a hereditary CRC syndrome?

- Age of CRC diagnosis
- Tumor characteristics
- History of polyps
- Family history
- Risk model score
- Date of prior genetic testing

When to test for a hereditary CRC syndrome?

- **Age of CRC diagnosis**
- Tumor characteristics
- History of polyps
- Family history
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All patients with colorectal cancer diagnosed before age 50 should be sent for genetic testing, regardless of family history or tumor characteristics

Stoffel et al., *Gastroenterology*, 2018

- 1 in 5 carries a germline mutation associated with cancer
- Half of patients may not have a “suspicious” family history

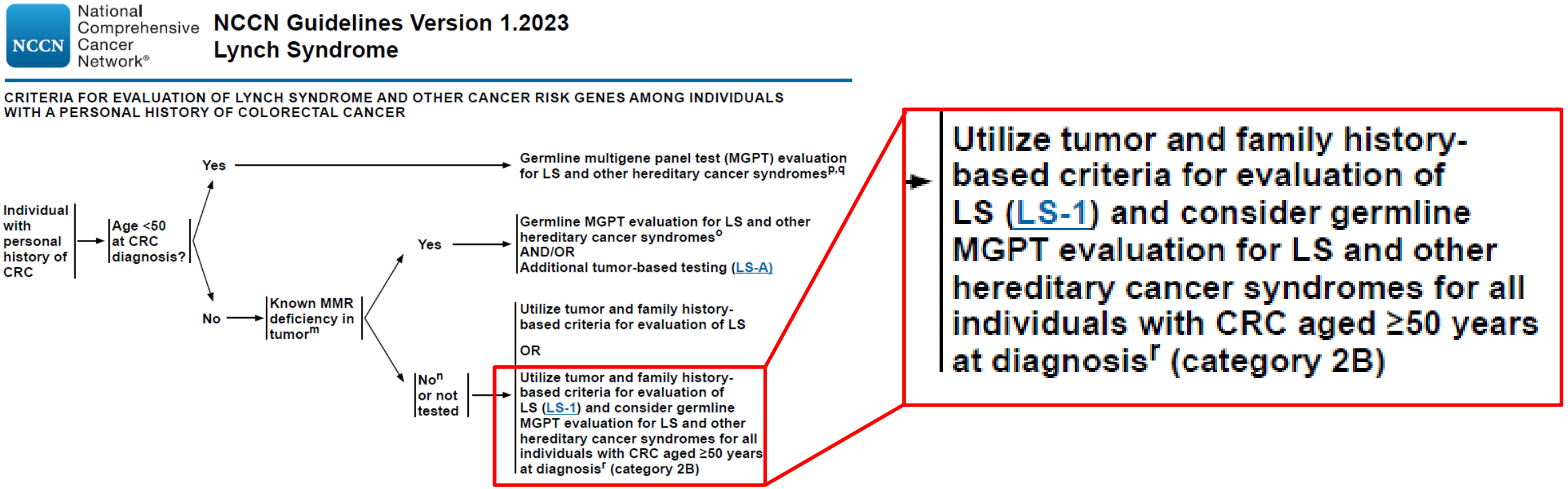
Seagle et al., *JCO*, 2023

- 12.2% with a pathogenic germline variant

When to test for a hereditary CRC syndrome?

- Age of CRC diagnosis
- **Tumor characteristics**
- History of polyps
- Family history
- Risk model score
- Date of prior genetic testing

1. Deficient MMR IHC - not explained by MLH1 hypermethylation
2. MSI-H
3. Potential germline hit(s) on a somatic tumor sequencing panel
4. **Possibly for ALL colorectal cancers**



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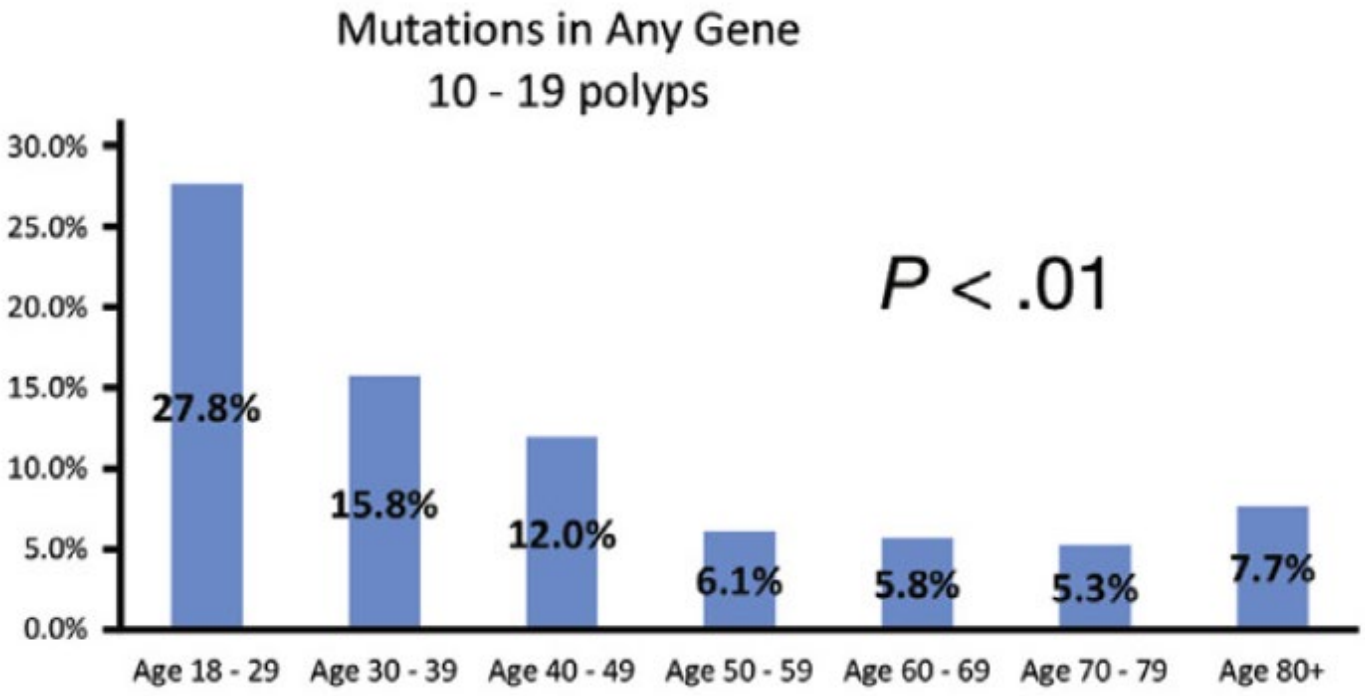

≥ 10 cumulative colonic adenomas

≥ 2 gastrointestinal hamartomas

≥ 5 serrated polyps proximal to rectum

Duodenal adenomas

Advanced fundic gland polyposis

You're just not comfortable with the patient's polyp burden!

Stanich, P.P., et al., *CGH*, 2019

When to test for a hereditary CRC syndrome?

- Age of CRC diagnosis
- Tumor characteristics
- History of polyps
- **Family history**
- Risk model score
- Date of prior genetic testing

Have a relative with a known hereditary cancer risk syndrome

Have a deceased relative with a suspected hereditary cancer risk syndrome or early onset cancer

Have a family history of CRC or other Lynch syndrome-related cancers

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Lynch Syndrome

- An individual with a LS-related cancer[b] and any of the following:
  - 1 first-degree or second-degree relative with an LS-related cancer[b] diagnosed <50 y
  - ≥2 first-degree or second-degree relatives with an LS-related cancer[b] regardless of age
- Family history[c] of any of the following:
  - ≥1 first-degree relative with a colorectal or endometrial cancer diagnosed <50 y
  - ≥1 first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer[b] regardless of age
  - ≥2 first-degree or second-degree relatives with LS-related cancers[b] including ≥1 diagnosed <50 y
  - ≥3 first-degree or second-degree relatives with LS-related cancers[b] regardless of age

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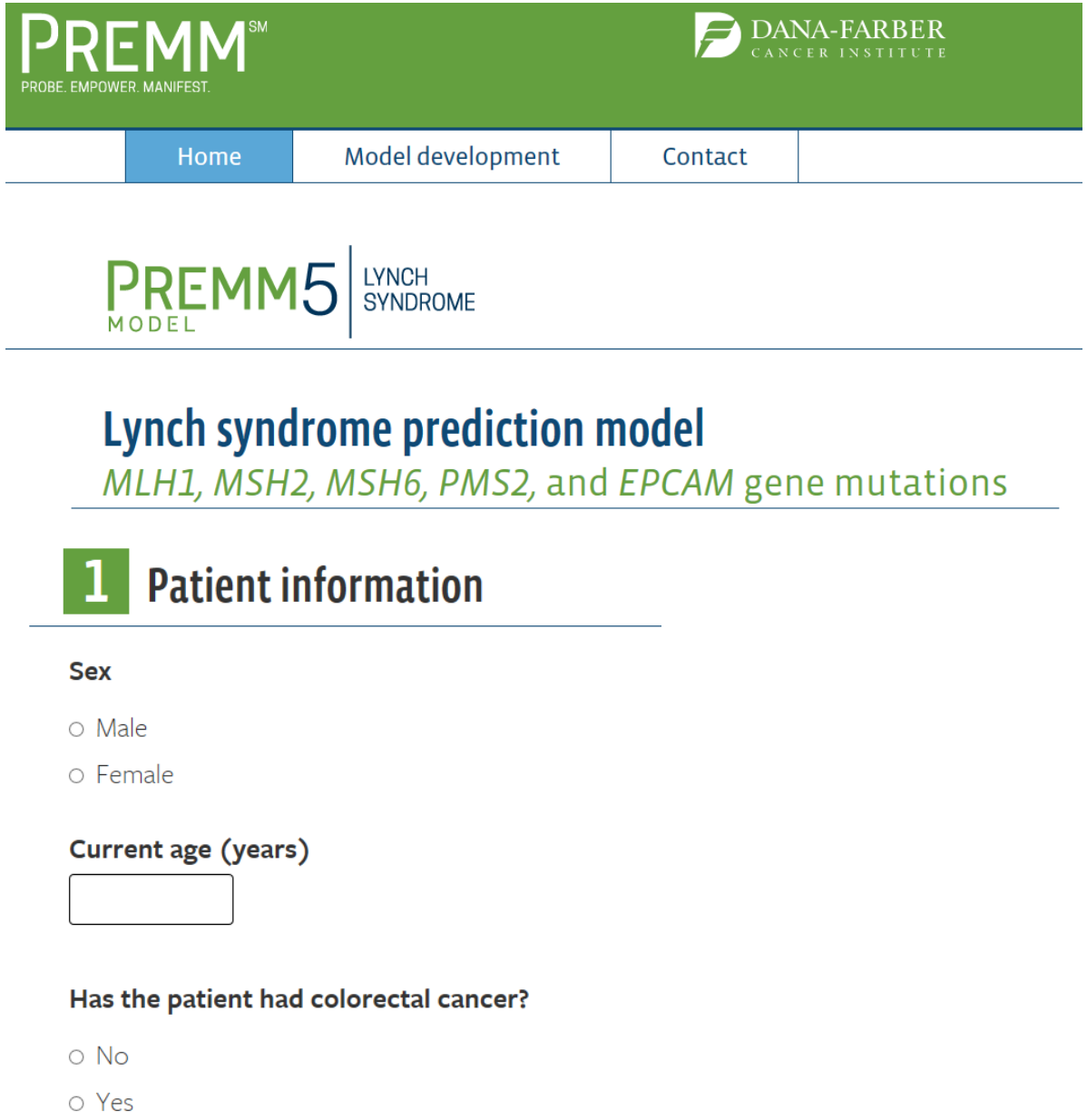
- Tumor characteristics
- History of polyps
- Family history
- **Risk model score**
- Date of prior genetic testing



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

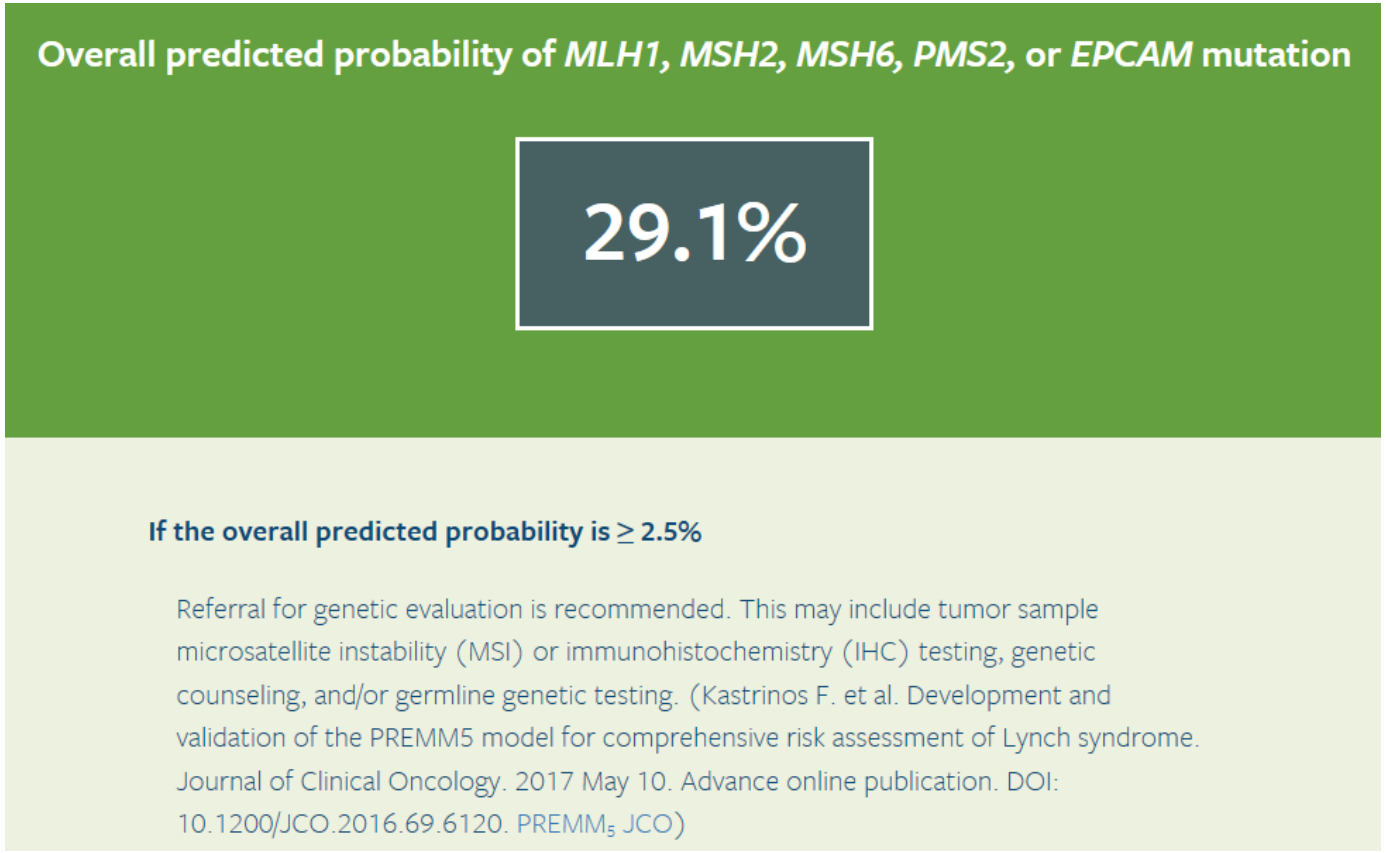
When to test for a hereditary CRC syndrome?

- Age of CRC diagnosis
- Tumor characteristics
- History of polyps
- Family history
- **Risk model score**
- Date of prior genetic testing

Risk ≥ 5% → Definitely test

Risk ≥ 2.5% → Consider testing

- Example family:
  - Proband is a male patient with CRC at age 40
  - Family history significant for a first degree relative with CRC at age 40



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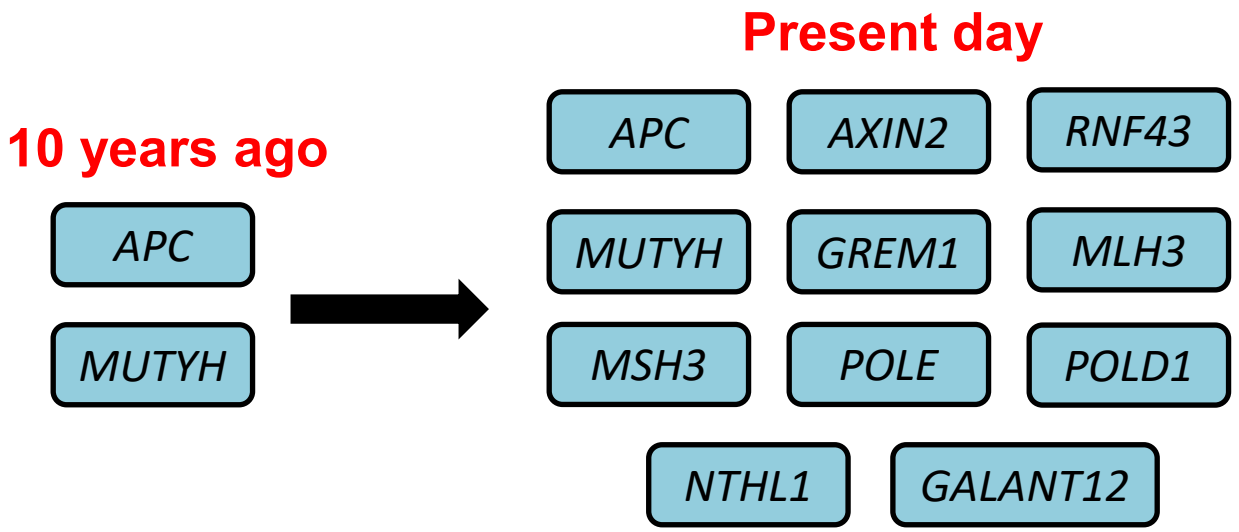
When to test for a hereditary CRC syndrome?

- Age of CRC diagnosis
- Tumor characteristics
- History of polyps
- Family history
- Risk model score
- **Date of prior genetic testing**

Individuals with older (often more limited) genetic testing may be eligible for updated testing

Non-hamartomatous polyposis evaluation



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CRC MGPT results amongst US cohorts

Study	CRC patients that got testing	Yield of PGVs	Panel size
Yurgelun, *JCO*, 2017	1058	9.9%	25 genes
AlDubayan, *AJHG*, 2018	680	9.4%	40 genes
LaDuca, *GIM*, 2019	8907	11%	5-49
Pearlman, *JCO PO*, 2021	3300 (1462 got testing [44%])	7.1%	25-66 genes
Uson, *CGH*, 2022	361	15.5%	84 genes

CRC MGPT results amongst US cohorts

Study	CRC patients that got testing	Yield of PGVs	Panel size	# Centers	% White	# Non-White participants
Yurgelun, *JCO*, 2017	1058	9.9%	25 genes	1	88.8%	107
AlDubayan, *AJHG*, 2018	680	9.4%	40 genes	1	98%	13
LaDuca, *GIM*, 2019	8907	11%	5-49	Multiple	??	??
Pearlman, *JCO PO*, 2021	3300 (1462 got testing [44%])	7.1%	25-66 genes	51 (1 state)	89.3%	331
Uson, *CGH*, 2022	361	15.5%	84 genes	3	82%	52

Therefore we need studies to determine the yield of MGPT across a large, more diverse CRC cohort

Methods

original reports

CANCER GENETICS

Multigene Panel Testing Yields High Rates of Clinically Actionable Variants Among Patients With Colorectal Cancer

Sarah E. Coughlin, MD[1]; Brandie Heald, MS[2]; Dana Farengo Clark, MS[1]; Sarah M. Nielsen, MS[2]; Kathryn E. Hatchell, PhD[2]; Edward D. Esplin, MD, PhD[2]; and Bryson W. Katona, MD, PhD[1]

JCO® Precision Oncology

2022

- A retrospective cohort of patients with reported CRC who underwent MGPT at a commercial laboratory between 03/2015-05/2021 (N=36,647)

- **Clinically actionable** variant in a gene associated with:
  - **CRC or polyposis** risk
  - Another hereditary cancer syndrome with clinical management and/or therapeutic implications (**other actionable**)

- **Non-actionable**
  - Variant in a gene without associated clinical management or therapeutic implications (including *MUTYH* monoallelic carriers)

Cohort Characteristics

TABLE 1. Cohort Characteristics of Patients With CRC Undergoing Multigene Panel Testing

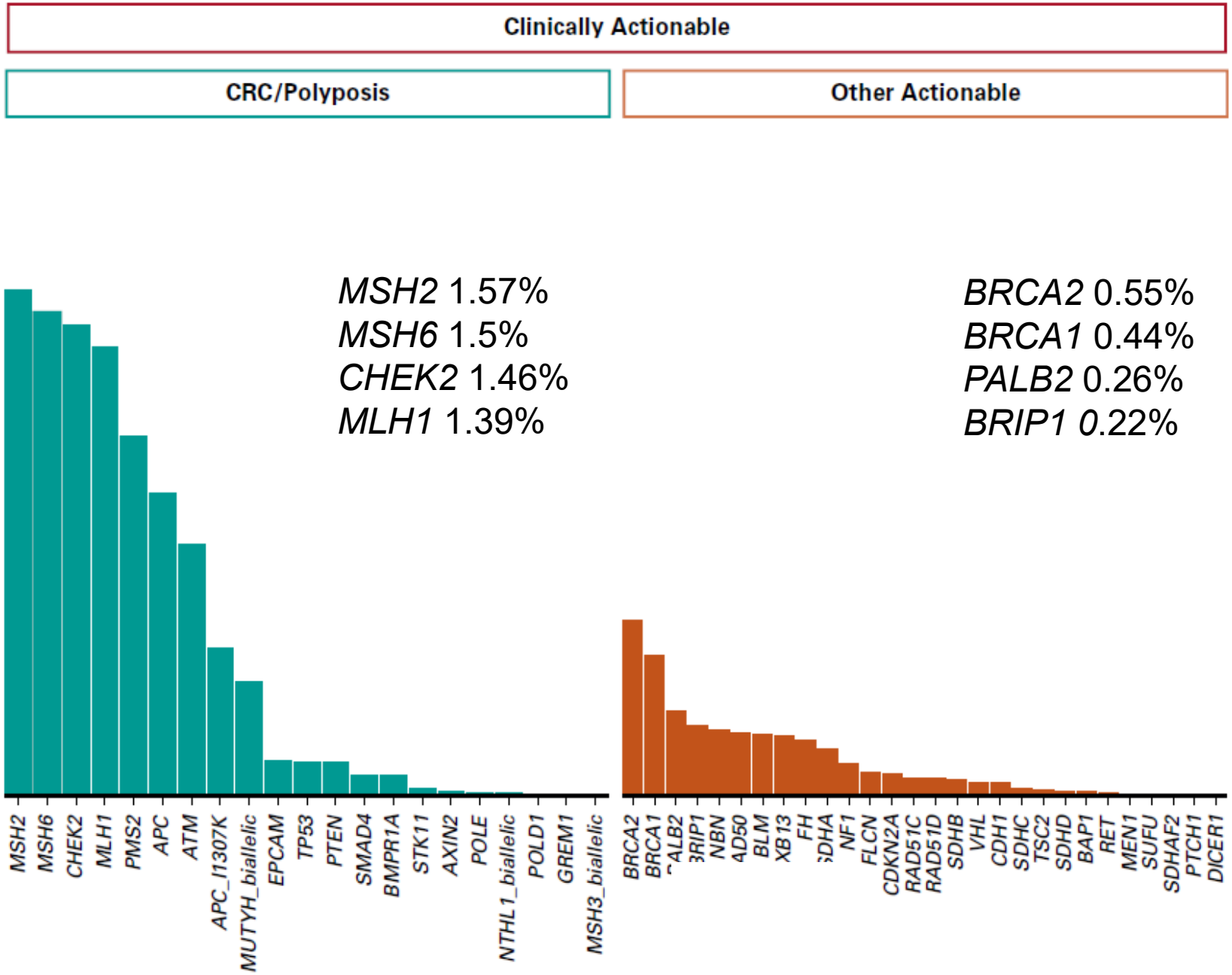
Characteristic	N = 34,244
Age at testing, years, No. (%)	
< 30	808 (2.4)
30-39	3,139 (9.2)
40-49	6,705 (19.6)
50-59	7,514 (21.9)
60-69	8,161 (23.8)
70-79	5,893 (17.2)
≥ 80	2,024 (5.9)
Female sex, No. (%)	20,792 (60.7)
Race/Ethnicity, No. (%)	
Ashkenazi Jewish	572 (1.7)
Asian	1,114 (3.3)
Black	2,277 (6.7)
Hispanic	1,905 (5.6)
Other or unknown	4,194 (12.2)
White	24,182 (70.6)
Number of genes tested, No. (%)	
11-20	4,706 (13.7)
21-30	3,613 (10.6)
31-40	1,597 (4.7)
41-50	11,243 (32.8)
51-80	3,027 (8.8)
> 80	10,058 (29.4)

MGPT Results

TABLE 2. Type and Number of Variants Identified by Multigene Panel Testing

Variant	N = 34,244, No. (%)
Patients with any PGV identified	4,864 (14.2)
Clinically actionable	4,059 (11.9)
CRC/polyposis	3,111 (9.1)
Other actionable	1,048 (3.1)
Nonactionable	952 (2.8)
PGV per patient	
1	4,146 (12.1)
2	441 (1.3)
3	20 (0.06)
> 3	1 (0.00)
Patients with a VUS identified	13,094 (38.2)
VUS and a PGV	1,751 (5.1)
VUS alone	11,343 (33.1)

Pathogenic Gene Variants



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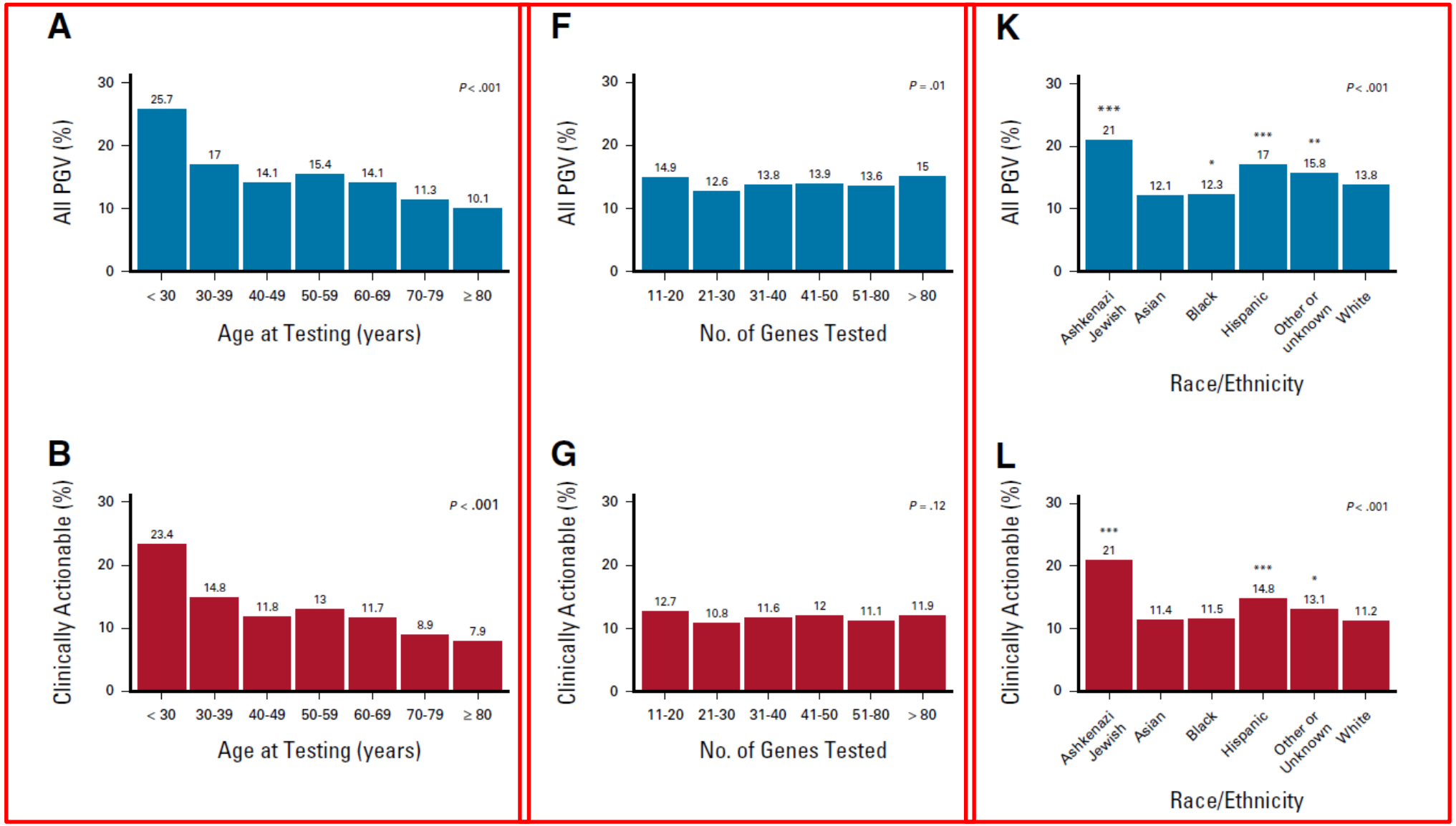
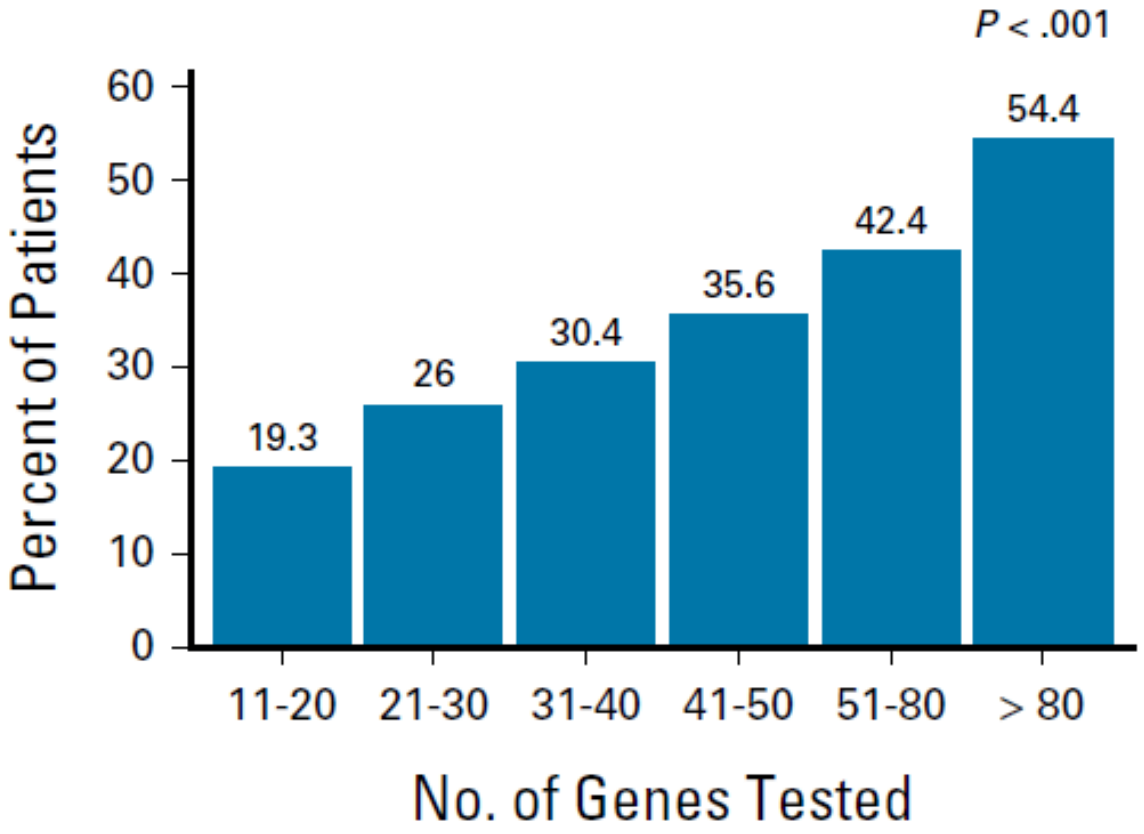
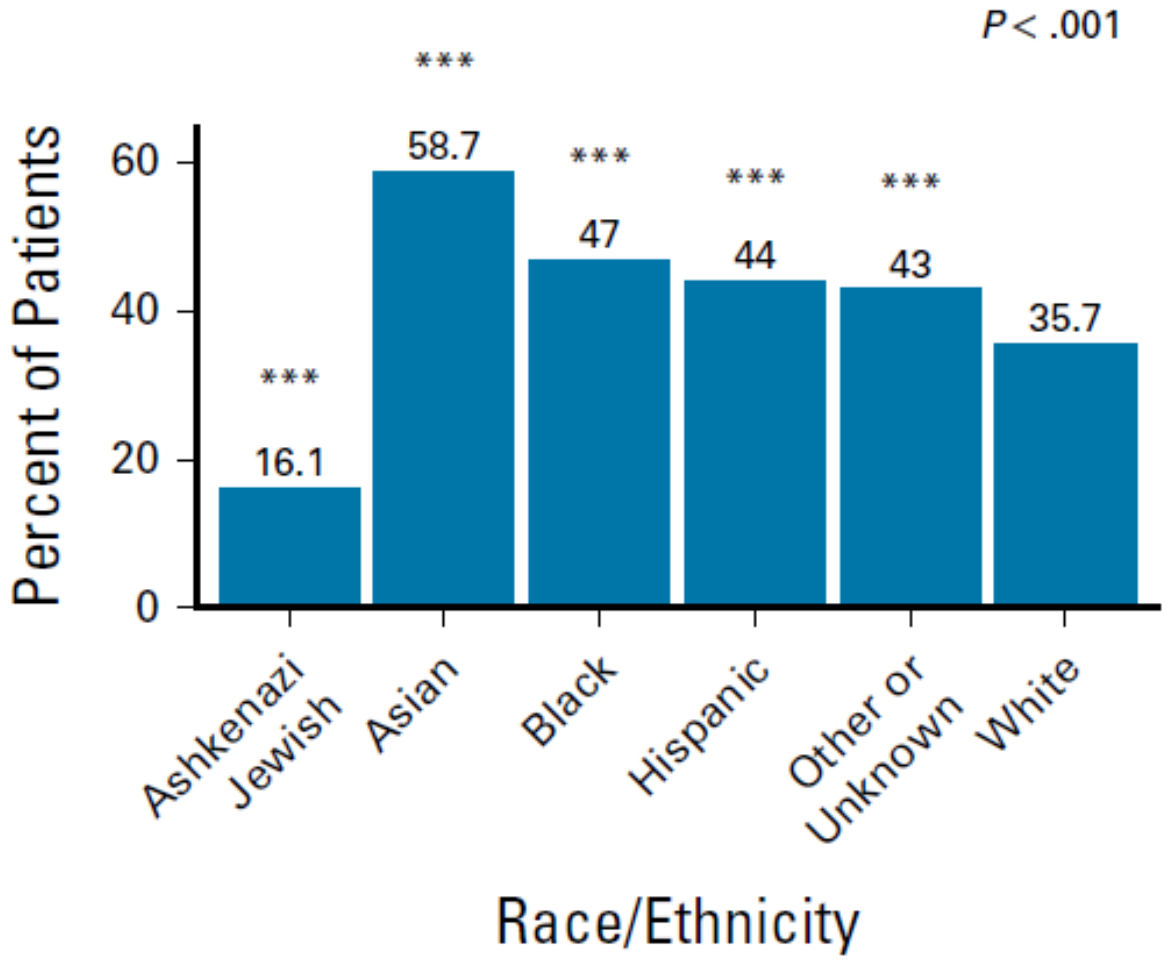


VUSs


P < .001
Percent of Patients
60
50
40
30
20
10
0
19.3
26
30.4
35.6
42.4
54.4
11-20
21-30
31-40
41-50
51-80
> 80
No. of Genes Tested


P < .001
Percent of Patients
60
40
20
0
***
16.1
***
58.7
***
47
***
44
***
43
35.7
Ashkenazi Jewish
Asian
Black
Hispanic
Other or Unknown
White
Race/Ethnicity

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Universal germline genetic testing for all CRC patients?

- **Pros** to testing all CRC patients
  - Identify CRC-risk variants
  - Identify variants that increase risk of other cancers
  - Allows cascade testing in family members
  - Rate of genetic variants found is similar to other cancers where universal testing is recommended (ie pancreatic cancer, high-risk prostate cancer)
  - MMR IHC is not perfect
  - Simplifies the referral process
  - Decrease disparities?

- **Cons** to testing all CRC patients
  - Cost
  - Genetic counseling and physician resources
    - ~150k new cases per year in the US, > 1 million survivors in the US
  - Management of VUSs
  - Does not add therapeutic value for CRC patients (unlike MMR IHC)
  - Increase disparities?

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Take home points

- ~10-15% of CRC patients who have germline genetic testing will have a PGV
- Many PGVs identified are not in classic CRC risk genes, but may have important implications
- Criteria for testing CRC patients is expanding
- Universal testing for all CRC patients is likely not far down the road

Thank you!

www.pennmedicine.org/GICancerGenetics

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University of Pennsylvania

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