MAYO CLINIC | School of Continuous Professional Development

APPROACH TO HEREDITARY (COLORECTAL) CANCER

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Florida ASCO
Puerto Rico Oncology Symposium, Feb 2023

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

- Jansen Research and Development
- Cancer Prevention Pharmaceuticals
- Recursion Pharmaceuticals

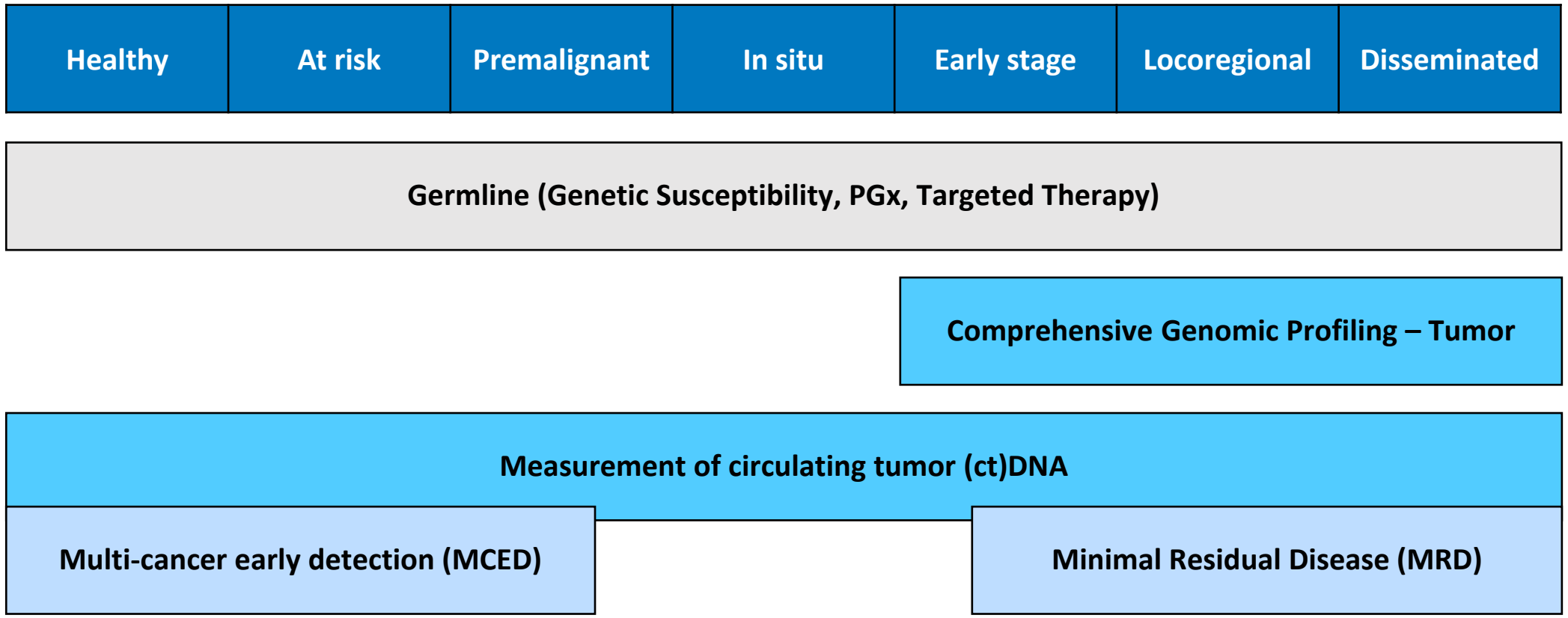
REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

LEARNING OBJECTIVES

- Review the role of cancer genetic assessment
- Explore a case to highlight approach to hereditary colorectal cancer, family history, genetic testing, interpretation of results

GENOMICS THROUGH THE CANCER JOURNEY



44-YEAR-OLD FEMALE PRESENTS FOR DIAGNOSTIC COLONOSCOPY

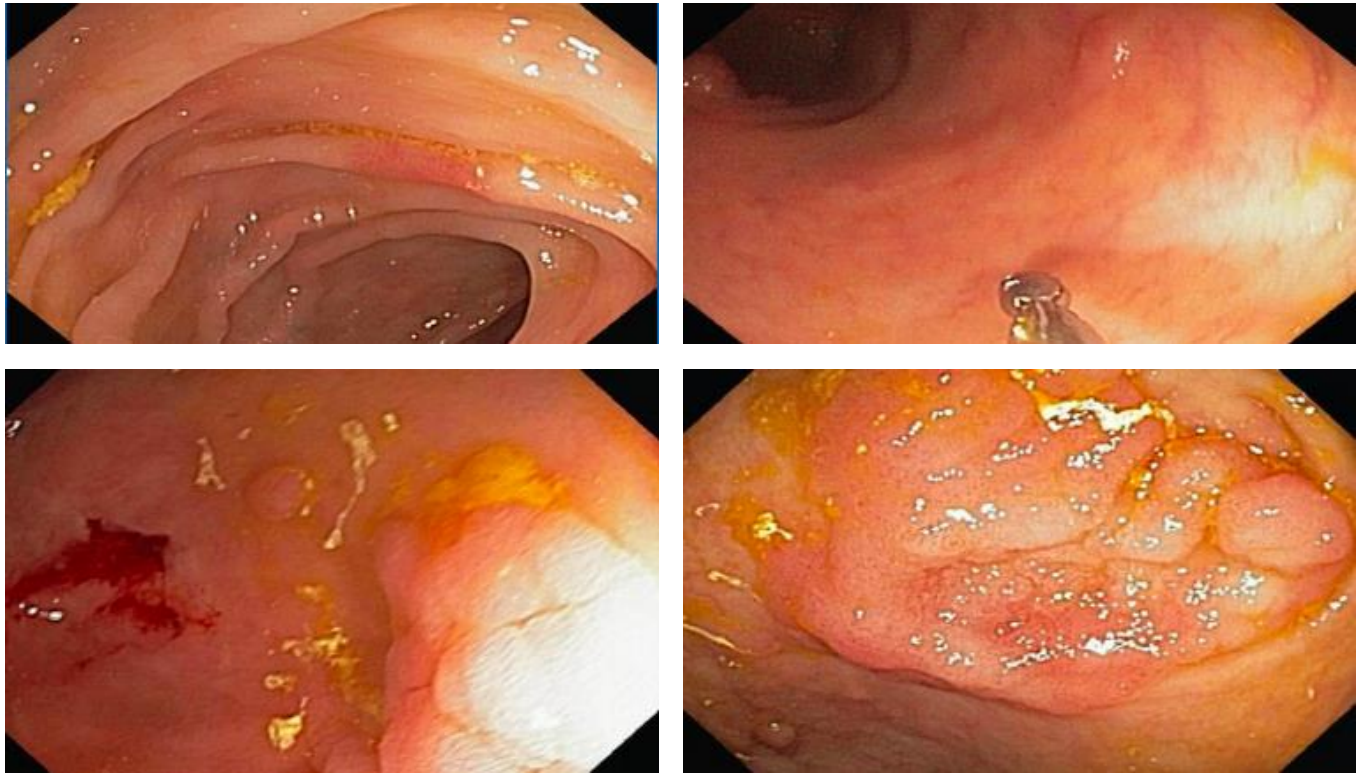
Initial Colonoscopy

- Performed at age 44 years for minor rectal bleeding
- Past medical/surgical history/medications: none
- Family history: denies CRC in parents, siblings; older brother with “polyps”
- Social History: nonsmoker, rare alcohol use
- Findings:

COLONOSCOPY FINDINGS

Endoscopic findings:

- 8 polyps, all <1cm throughout the colon
- Two flat >1.5cm polyps in the cecum; unable to perform a saline lift of one at the appendiceal orifice, biopsies taken



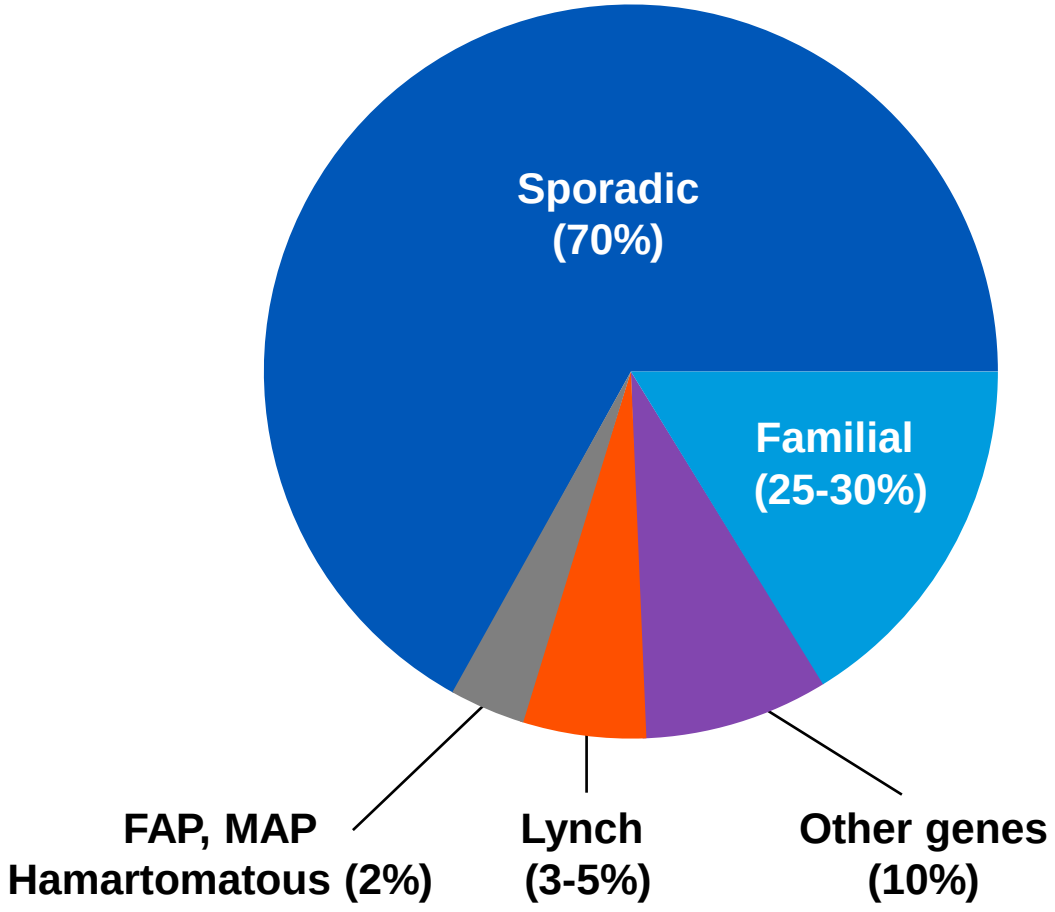
COLONOSCOPY FINDINGS

Pathology report:

- Polyp histology
  - Six tubular adenomas without high-grade dysplasia
  - Two hyperplastic polyps
- Histology of flat polyps in the cecum
  - Biopsies from the polyps consistent with tubulovillous adenoma
  - Polyp at the appendiceal orifice with focus of invasive carcinoma

What is the differential diagnosis?

COLORECTAL CANCER



Redrawn from: Burt RW et al. Prevention and Early Detection of CRC, 1996

HEREDITARY CRC SYNDROMES

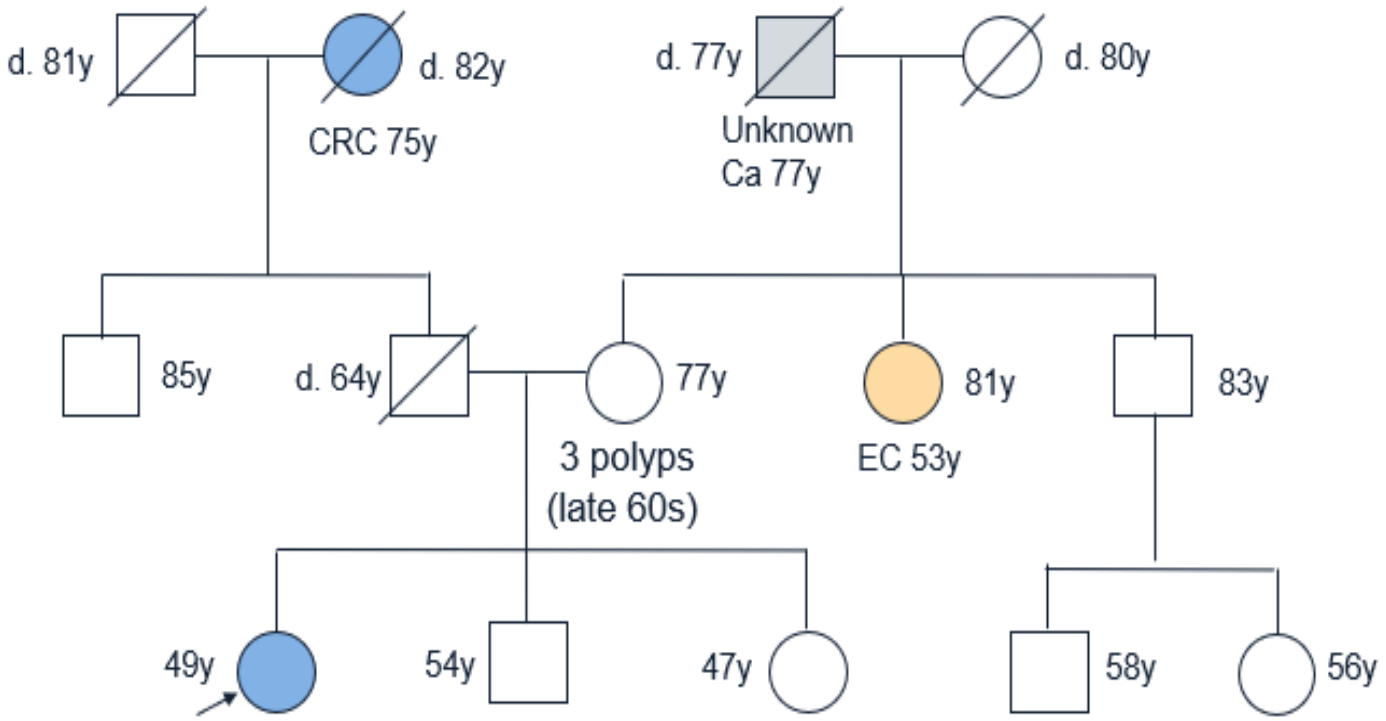
* Autosomal recessive

Syndrome	Gene(s)	Features
Lynch Syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	CRC, endometrial/ovarian, urothelial, brain, small bowel, skin (sebaceous adenoma/carcinoma)
Familial Adenomatous Polyposis	APC	Adenomas, CRC, duodenal, gastric and thyroid cancer, osteomas, soft tissue tumors, desmoid tumors
MYH-Associated Polyposis*	MUTYH	Adenomas, CRC, thyroid ca, duodenal polyposis/ca
NTHL1- associated polyposis*	NTHL1	Adenomas (oligopolyposis), endometrial, CRC
Polymerase proofreading associated polyposis	POLE, POLD1	Adenomas (oligopolyposis), endometrial, brain cancer
MSH3- associated polyposis*	MSH3	Adenomas, duodenal adenomas, CRC and gastric cancer, early-onset astrocytoma.
Peutz-Jeghers Syndrome	STK11	Mucocutaneous pigmentation, hamartomas, breast, GI, pancreatic, and rare GYN/testicular cancers
PTEN Hamartoma Tumor Syndrome	PTEN	Intestinal hamartomas, glycogen acanthosis, skin lesions, macrocephaly, breast, thyroid, renal,endometrial cancers, and CRC
Juvenile Polyposis Syndrome	BMPR1A, SMAD4	Hamartomas, gastric and colon cancer, SMAD4 –HHT overlap

FAMILY HISTORY ASSESSMENT

Family history

- Important determinant of inherited cancer risk
- 3 generations*
- Cancer or other diseases
- Ages of cancer and death
- Ancestry/ethnicity
- Medical record verification of cancer/polyp in family members



TA polyps x6 (44y)
TA polyps x 9 (49y)
TVA + focus CRC (49y)

+"polyps"

GENETIC EVALUATION FOR COLORECTAL NEOPLASIA

Tumor/germline testing options

- Immunohistochemical (IHC) Testing or MSI
- Tumor somatic or CT-DNA
- Germline Next-generation sequencing (multi-gene panels)

Who to test?

- Patient unaffected by neoplasia versus affected family member

Determination of when germline genetic testing is indicated

- Clinical criteria vs Guide treatment options (ie. MMR, BRCA1,2)

Risks, benefits, and alternatives

- Cost
- Discrimination (health and life insurance, disability, employment)
- Disclosure of results
- Alternatives to testing

(PRIOR) INDICATIONS FOR GENETIC TESTING[1]

- CRC at age <50 years old (regardless of MSI status)*
- Multiple primary Lynch syndrome cancers
- CRC and family history of >1 FDR with CRC or Endometrial ca
- >10 cumulative colorectal adenomas *
- >3 cumulative hamartomatous polyps
- IHC tumor testing with MMR deficiency
- Risk Scores: PREMM5 or MMRpro
- Patients meeting other criteria for genetic testing

[1]Heald B et al Familial Cancer 2020

RAPIDLY CHANGING TIMES

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Lynch Syndrome

NCCN Guidelines Index
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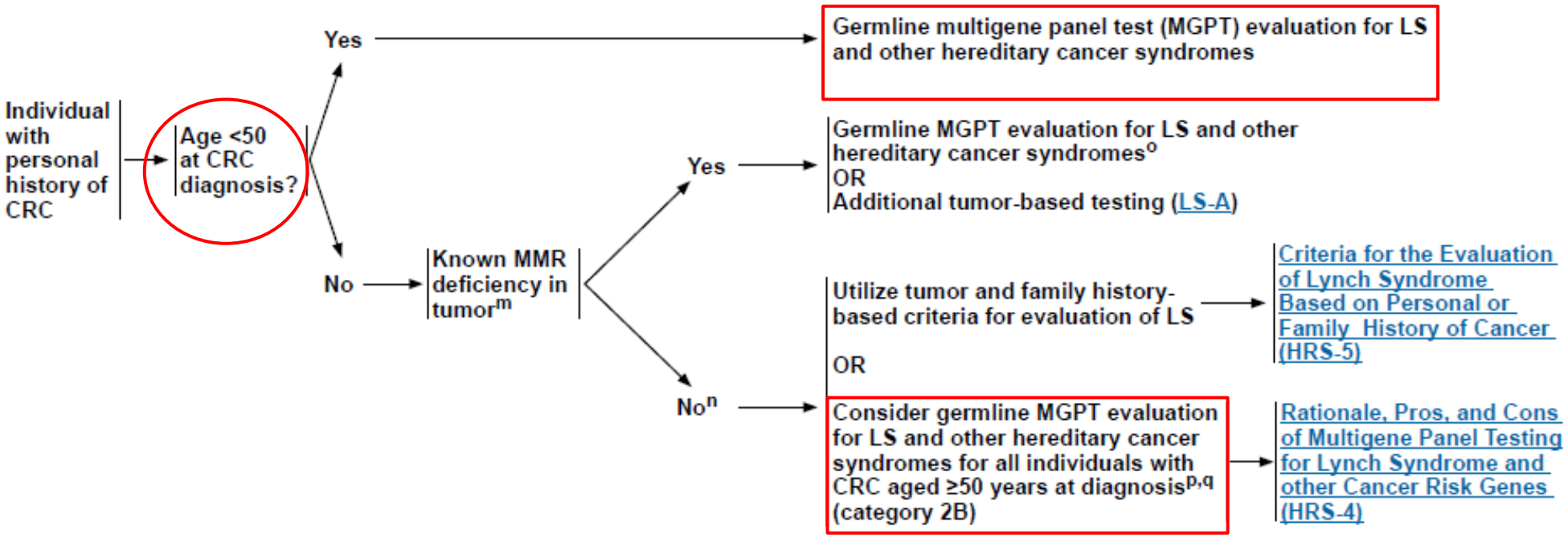
Discussion

CRITERIA FOR EVALUATION OF LYNCH SYNDROME AND OTHER CANCER RISK GENES AMONG INDIVIDUALS WITH A PERSONAL HISTORY OF COLORECTAL CANCER

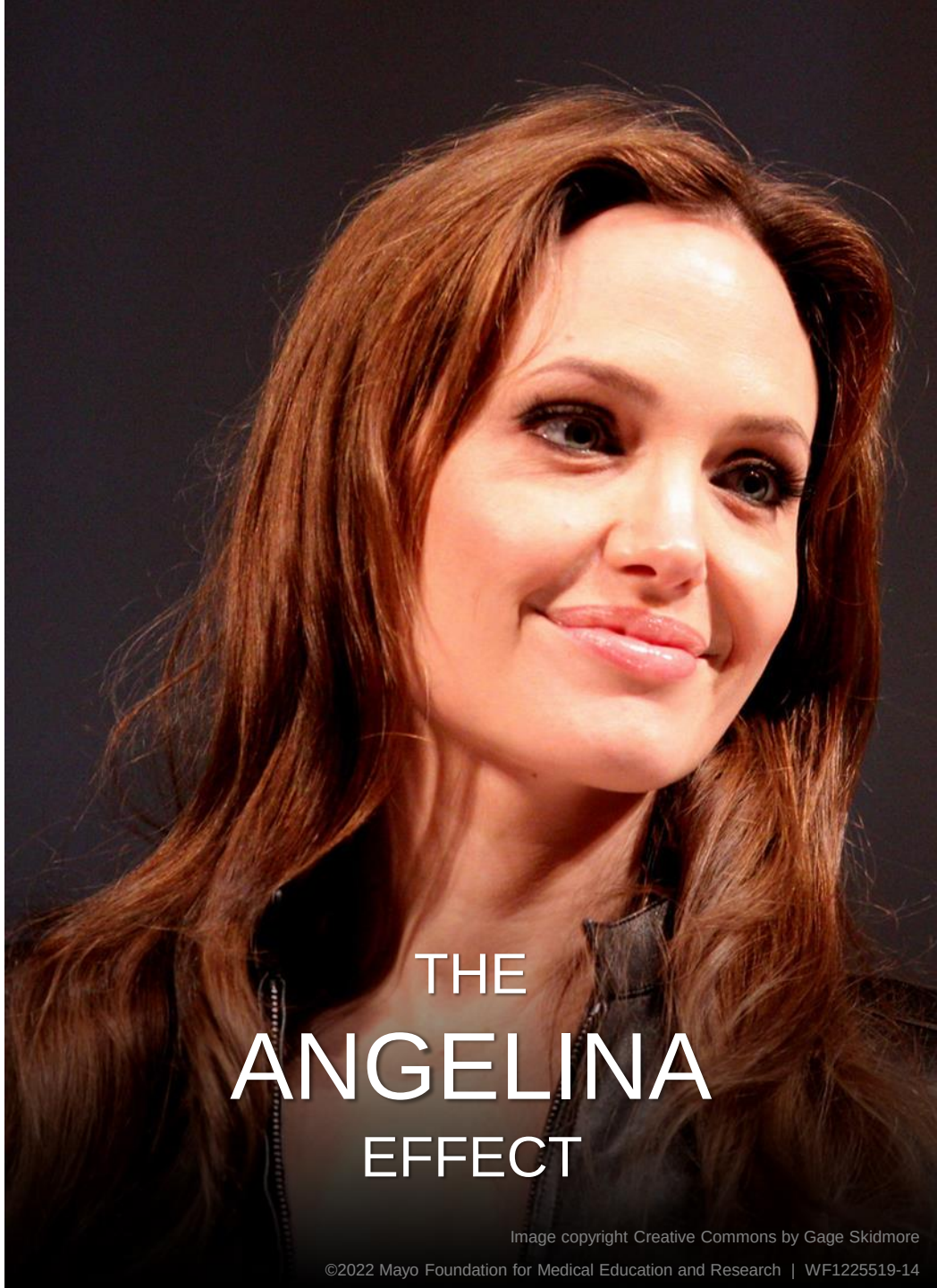


GINA & YOUR HEALTH INSURANCE

- GINA makes it against the law for health insurers to request, require, or use genetic information to make decisions about:
  - Your eligibility for health insurance
  - Your health insurance premium, contribution amounts, or coverage terms

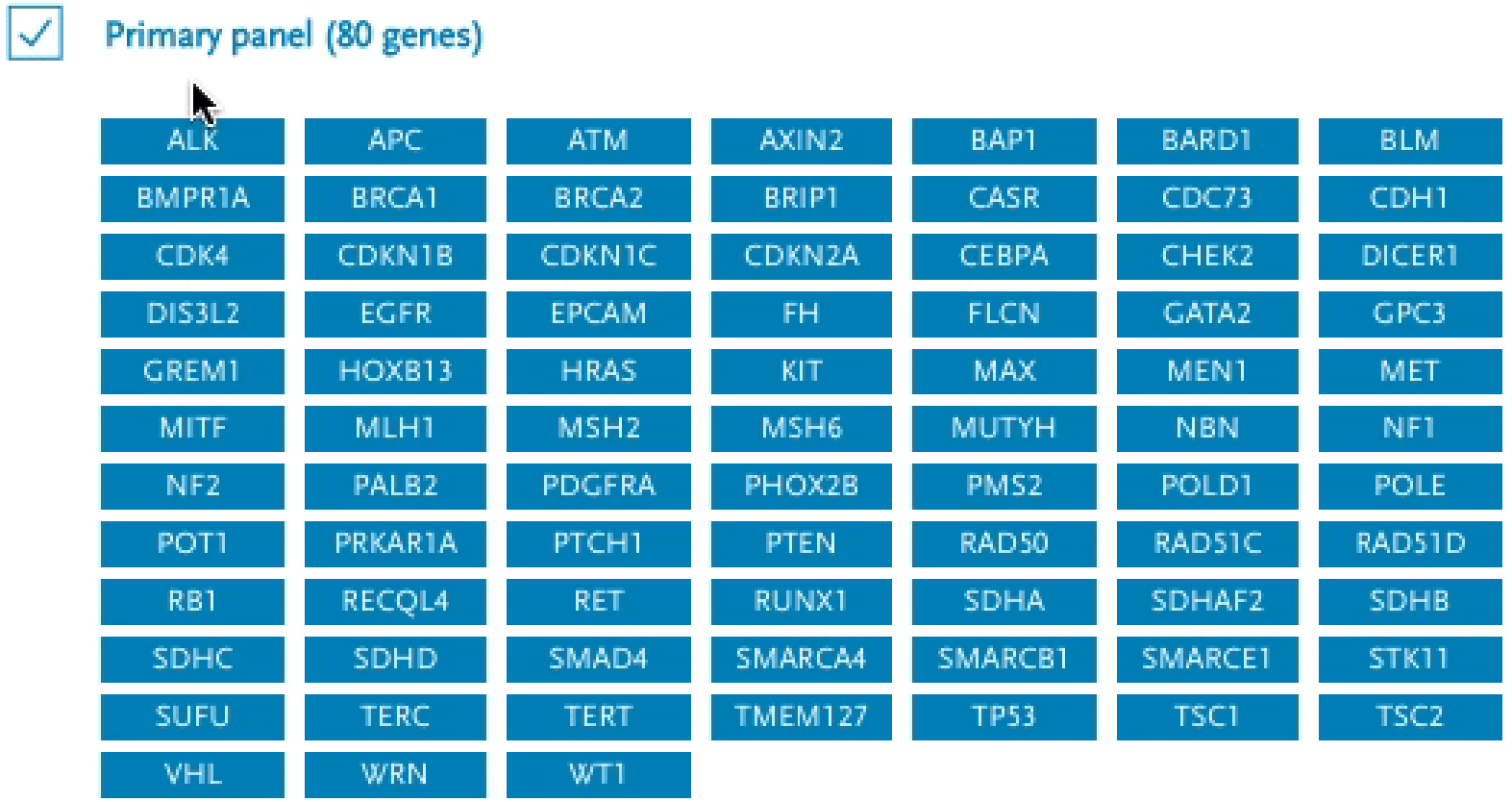
This means it is against the law for your health insurer to use genetic test result or family health history as a reason to deny you health insurance or decide how much you pay for your health insurance.

- In addition, GINA makes it against the law for your health insurer to:
  - Consider family history or a genetic test result a pre-existing condition
  - Ask or require that you have a genetic test
  - Use any genetic information they do have to discriminate against you, even if they did not mean to collect it



GENETIC TESTING

Multigene cancer panel performed

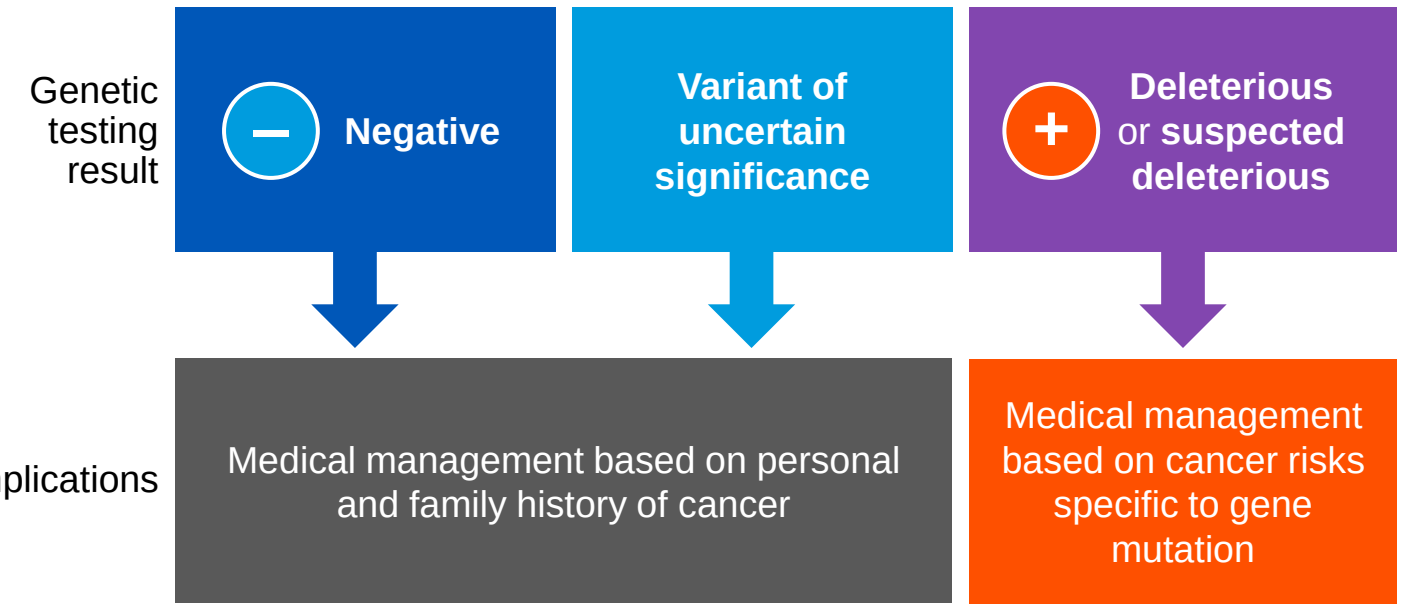


MULTIGENE CANCER PANEL TESTING

- Multiple genes sequenced simultaneously
- Multigene panels types
  - Disease-specific, guideline-specific, comprehensive
- Advantages & disadvantages
- Cascade testing: at-risk relatives undergo single-site genetic testing for the newly identified familial gene variant

IMPLICATIONS OF GENETIC TESTING

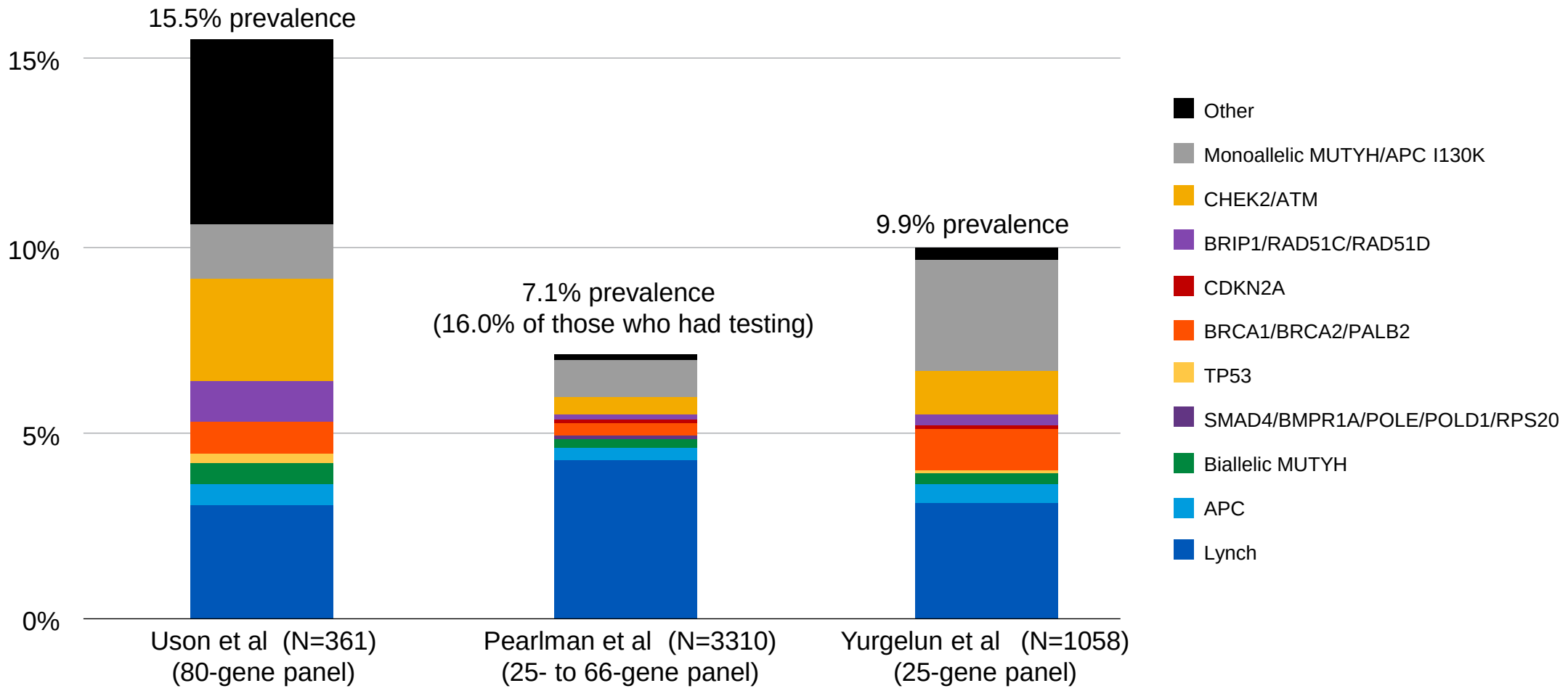
Types of results



- Preliminary evidence genes, possibility of no guidelines
- Psychological/psychosocial impacts of results
- Genetic discrimination - GINA

Redrawn from presenter-supplied original; no source supplied.

OUTCOMES OF MULTIGENE PANEL TESTING IN CRC



Redrawn from: Uson PLS, et al. Clin Gastroenterol Hepatol 2021; ePub.
Pearlman R, et al. JCO Precis Oncol 2021;5:779-91. Yurgelum MD, et al. J Clin Oncol 2017;35:1086-95.

GENETIC TESTING RESULTS

RESULT: POSITIVE

One pathogenic variant identified in MSH2. MSH2 is associated with autosomal dominant Lynch syndrome and autosomal recessive constitutional mismatch repair deficiency syndrome.

Additional variant(s) of uncertain significance identified

Gene	Variant	Zygosity	Variant classification
MSH2	c.1216C>T (p.Arg406*)	Heterozygous	Pathogenic
PTEN	c.1160>T (p.Pro387Leu)	Heterozygous	Uncertain significance

About this test

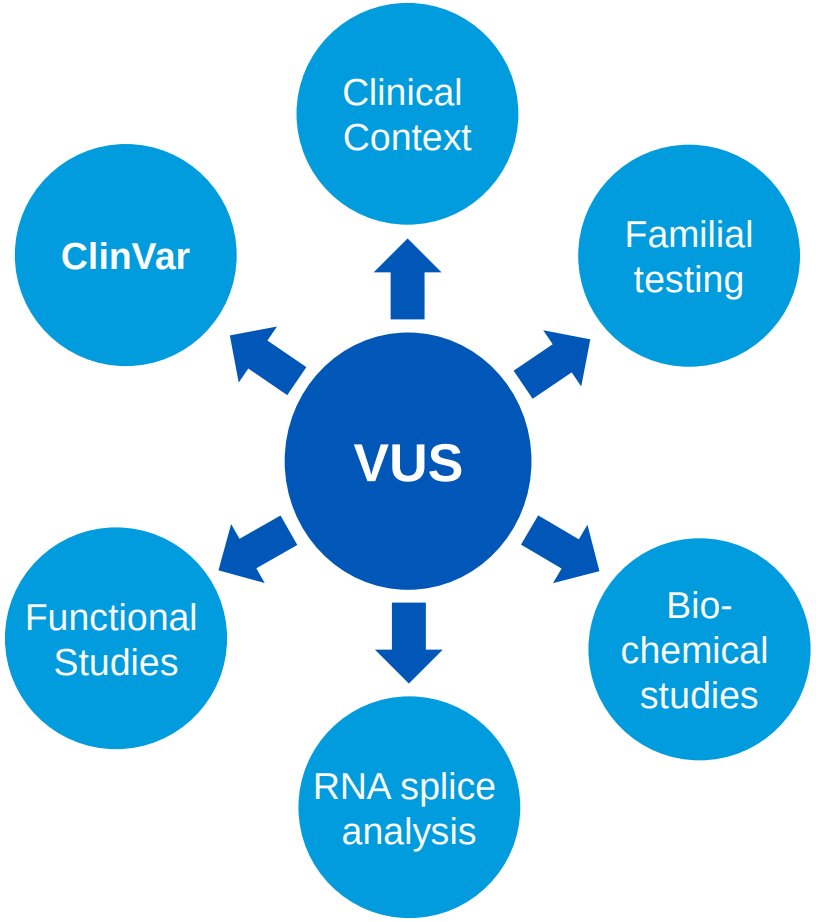
This diagnostic test evaluates **47 gene(s)** for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

MANAGEMENT OF OUR PATIENT WITH LYNCH SYNDROME

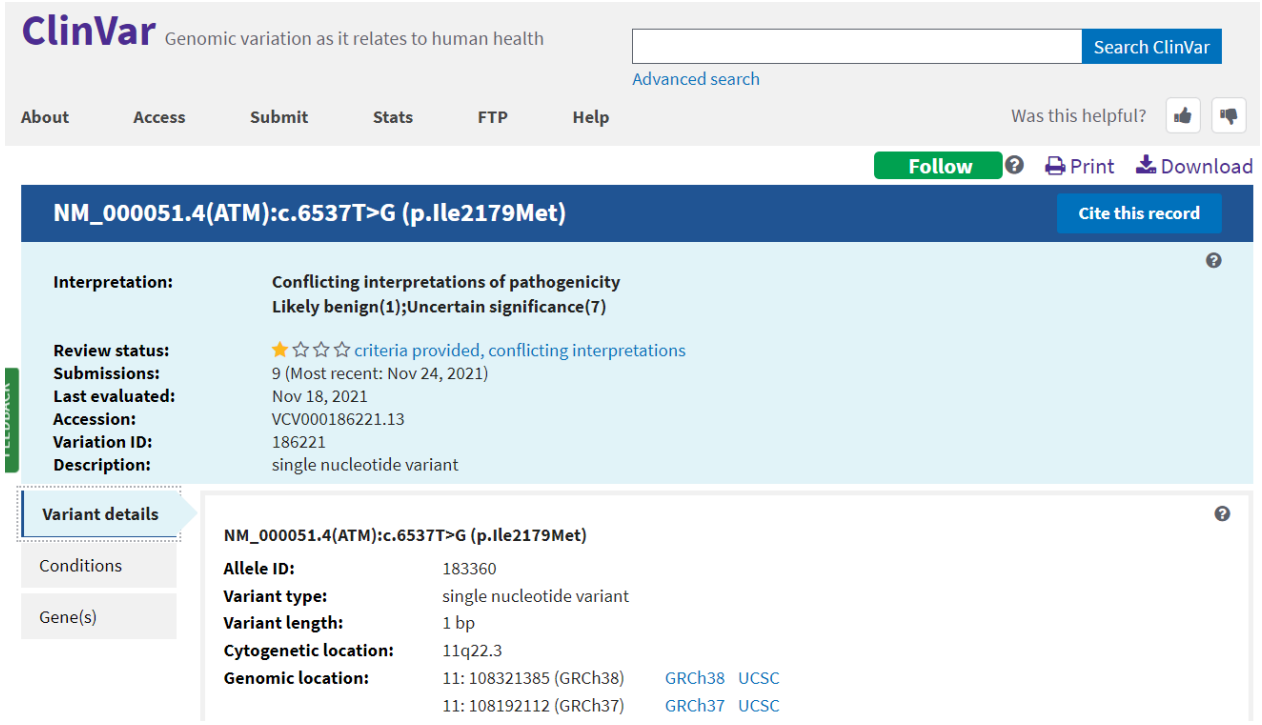
- Patient was referred for surgical evaluation
  - Colectomy with IRA vs Right Hemicolectomy
  - Endoscopic surveillance of rectum
- EGD
  - Did not identify gastric or duodenal (ampullary) polyps
- Non-GI related malignancies
  - Endometrial surveillance followed by TAH
- **Cascade testing for family members**
  - Brother also has Lynch syndrome

VARIANTS OF UNCERTAIN SIGNIFICANCE: CLASSIFICATION AND RE-CLASSIFICATION

- **Variants of uncertain significance**
  - Genetic sequence variant but there is not enough known about the change to categorize it
- VUS rates can approach 40-50%
  - Higher when using large panels
  - Higher rate in minority (non-white) populations



RESOLVING VUS: USING CLINVAR



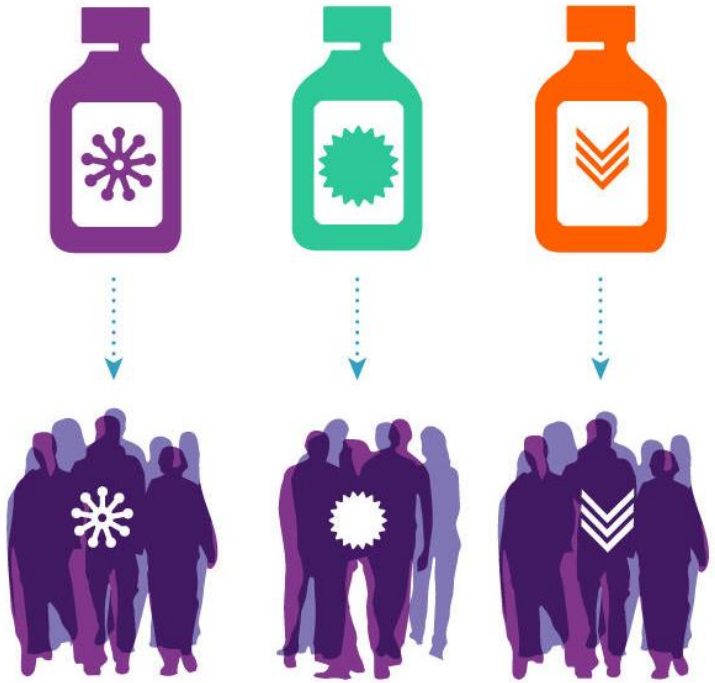
Submitted interpretations and evidence

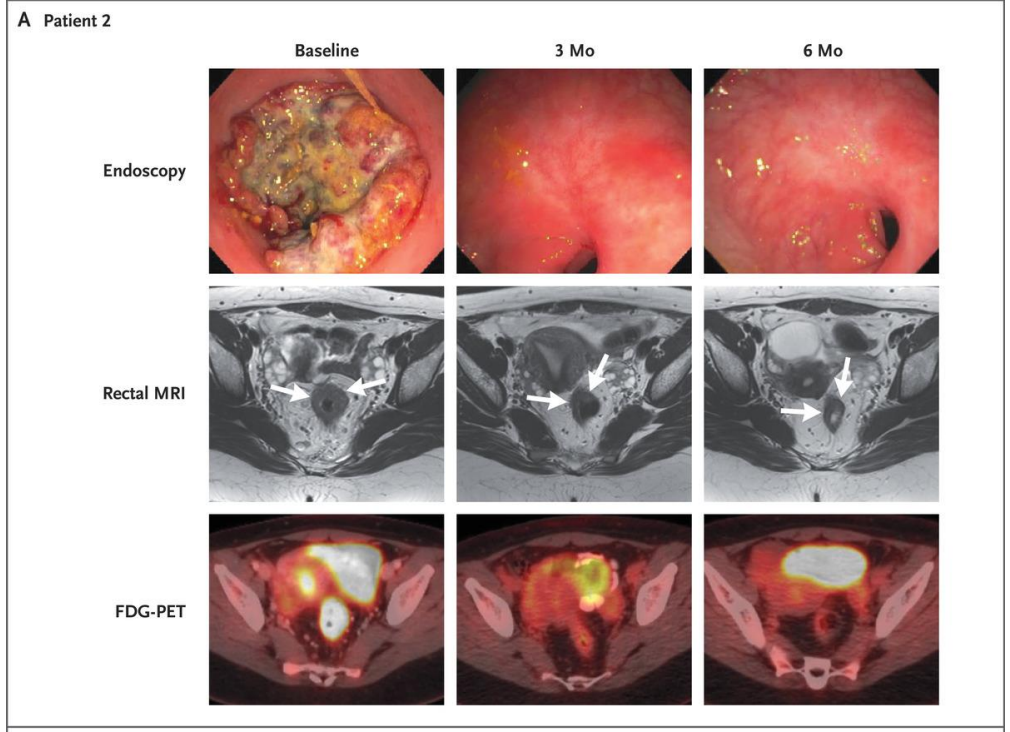
Interpretation (Last evaluated)	Review status (Assertion criteria)	Condition (Inheritance)	Submitter
Uncertain significance (Sep 29, 2020)	criteria provided, single submitter (Ambry Autosomal Dominant and X-Linked criteria (7/2020)) Method: clinical testing	Hereditary cancer-predisposing syndrome Affected status: unknown Allele origin: germline	Ambry Genetics Accession: SCV000216520.5 Submitted: (Nov 30, 2020)
Uncertain significance (Oct 28, 2020)	criteria provided, single submitter (Invitae Variant Classification Sherloc (09022015)) Method: clinical testing	Ataxia-telangiectasia syndrome Affected status: unknown Allele origin: germline	Invitae Accession: SCV000260111.9 Submitted: (Jan 07, 2021)
Uncertain significance (Nov 18, 2021)	criteria provided, single submitter (GeneDX Variant Classification (06012015)) Method: clinical testing	Not Provided Affected status: yes Allele origin: germline	GeneDx Accession: SCV000292476.12 Submitted: (Nov 24, 2021)

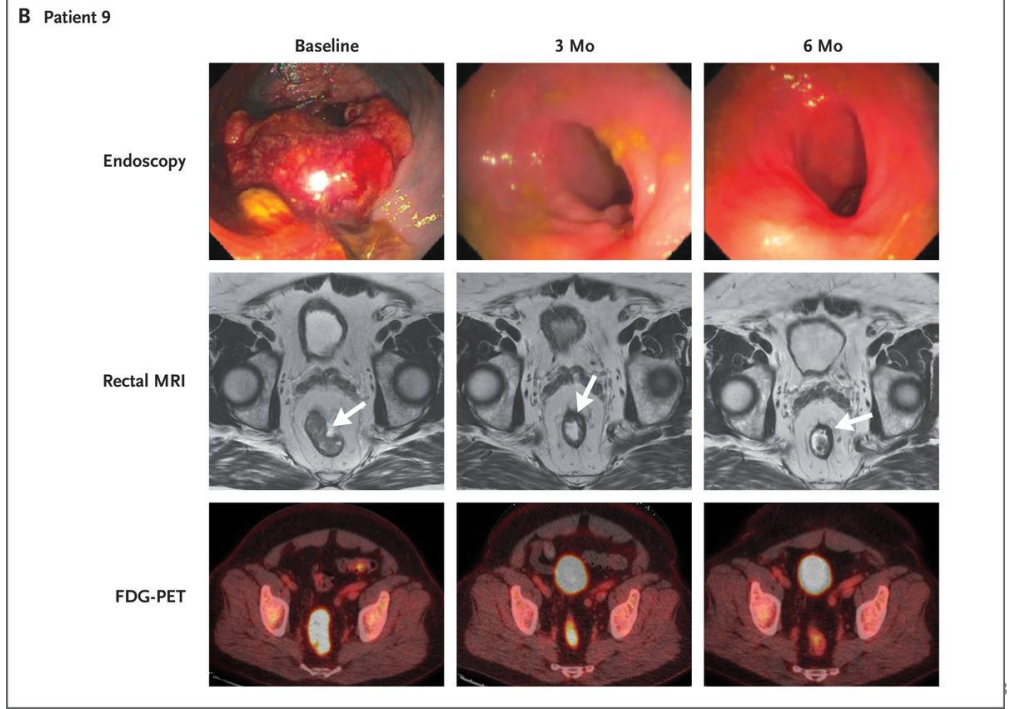
GERMLINE MUTATION STATUS: IMPACT ON TREATMENT RECTAL

Evolution of Endoscopic and Radiographic Response in Representative Patients Treated with Dostarlimab

Cercek et al. N Engl J Med 2022;386:2363-2376.







NOT JUST COLORECTAL!

NCCN GUIDELINES VERSION 1.2022 – HEREDITARY CANCER TESTING CRITERIA

Testing is clinically indicated in the following scenarios:

See General Testing Criteria on CRIT-1

Exocrine pancreatic cancers
- **All individuals diagnosed with exocrine pancreatic cancer**
- **First-degree relatives of individuals diagnosed with exocrine pancreatic cancer**

Neuroendocrine pancreatic tumors – See NCCN Guidelines for Neuroendocrine and Adrenal Tumors

Criteria met → **See GENE-1**

If testing criteria not met, consider testing for other hereditary syndromes → **If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines**

Principles of Genetic and Molecular/Biomarker Analysis

Germline testing is recommended in patients with a personal history of prostate cancer in the following scenarios:

By Prostate Cancer Stage or Risk Group (diagnosed at any age)
- **Metastatic, regional (node positive), very-high risk localized, high-risk localized prostate cancer**

By Family History and/or Ancestry

• ≥1 first-, second-, or third-degree relative with:	• Breast cancer at age ≤50 y • Colorectal or endometrial cancer at age ≤50 y • Male breast cancer at any age	• Ovarian cancer at any age • Exocrine pancreatic cancer at any age • Metastatic, regional, very-high-risk prostate cancer at any age
• ≥1 first-degree relative (father or brother) with:	• Prostate cancer at age ≤60 y	
• ≥2 first-, second-, or third-degree relatives with:	• Breast cancer at any age	• Prostate cancer at any age
• ≥3 first- or second-degree relatives with:	• Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer	
• A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, EPCAM		
• Ashkenazi Jewish ancestry		

Personal history of breast cancer

Redrawn from: National Comprehensive Cancer Network

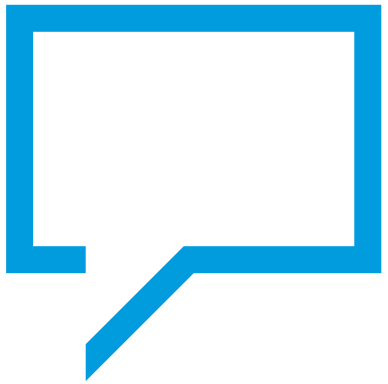
SUMMARY

- Hereditary cancer syndromes are not rare
  - Germline pathogenic variants are found in 10-30% of individuals with cancer
- Red flags for hereditary syndromes
  - Early onset neoplasia and/or
  - Numerous relatives with CRC, breast, pancreas or other cancers
- Extended family history assessment is recommended
  - Some syndromes are autosomal recessive
- Genetic risk assessment and genetic testing is a process and personal
  - Counseling (pre- and post-) genetic testing is critical
- Multigene panel testing is widely performed
  - Important to understand implications and potential shortcomings
  - Exome sequencing will identify Lynch and HBOC in populations

INTEGRATING CANCER GENOMICS INTO MAYO PRACTICE

- MCCC Personalized Medicine Office
  - Drs. Patnaik, Samadder & Katie Gano
  - Goal to assist the MCCC Practice integrate genomics into standard care
  - Partnership with Laboratory Medicine (MCL) and Center for Individualized Medicine
- somatic tumor, germline, ct-DNA
- Whole exome (genome) sequencing in practice
- Polygenic risk scores
- Transcriptome, RNA, metabolomics

QUESTIONS & ANSWERS



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THANK YOU!

Rochester, Minnesota

Phoenix, Arizona

Jacksonville, Florida