IDENTIFYING AND MANAGING LYNCH SYNDROME

DISCLAIMER

- This information is provided to help answer questions with respect to cancer risks, hereditary cancer risks and pre-dispositional cancer testing. It is general in nature and is not intended to provide a comprehensive, definitive analysis of specific risk factors for cancer or hereditary cancer risks. The information provided herein should not be relied upon; but rather, should be taken into consideration with other medical and research information regarding cancer risks, hereditary cancer risks and pre-dispositional cancer testing and risk factors.
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AT THE CONCLUSION OF THIS PRESENTATION, PARTICIPANTS SHOULD UNDERSTAND THE FOLLOWING RELATING TO LYNCH SYNDROME:

- Prevalence of Lynch syndrome
- Methods for identifying at risk individuals
- Clinical features and medical management options
- Appropriate interpretation of test results

LYNCH SYNDROME (ALSO KNOWN AS HEREDITARY NON-POLYPOSIS COLORECTAL CANCER: HNPCC)

- Population prevalence: ~1 in 300 - 1 in 500
- Associated with a significantly increased risk for colorectal and endometrial cancers
- Caused by mutations in the following genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*
- Autosomal dominant inheritance

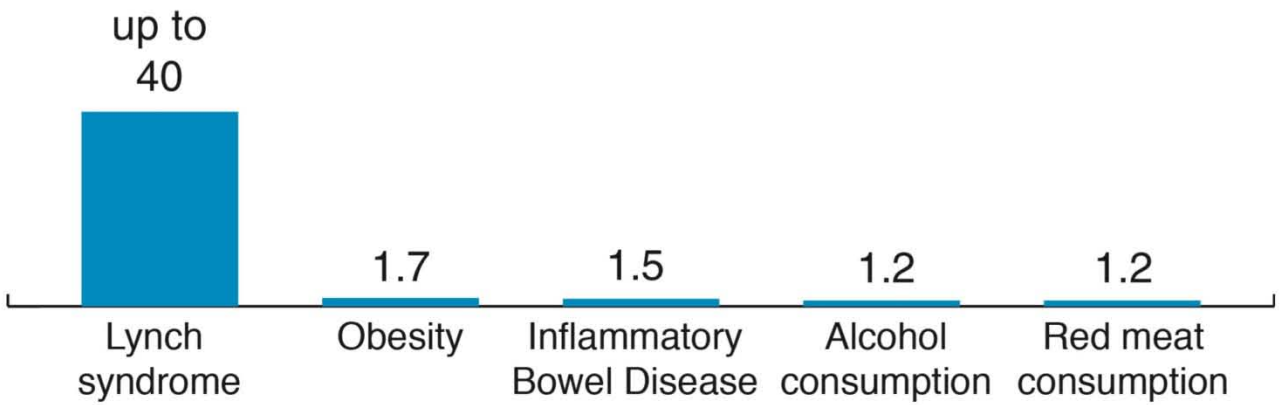
Gastroenterology 2010;138: 2197.
Surg Oncol Clin N Am 2009;18:687-703.
Nature Genetics 2009;41:112-7.

LYNCH SYNDROME IS THE SINGLE MOST COMMON EXPLANATION FOR HEREDITARY COLORECTAL CANCER

- ~2-4% of all colorectal cancer is due to Lynch syndrome
- ~6% of unselected colorectal cancer under age 50 is due to Lynch syndrome
- Average age of colorectal cancer onset in *MLH1/MSH2* carriers is 58 years (limiting analysis to those under age 50 will miss patients)
- Up to 24% of patients with colorectal cancer are at risk of having a hereditary colorectal cancer syndrome

N Engl J Med 2005;352:1851–1860.
J Clin Oncol 2000;18:2193–200.
Familial Cancer 2005;4:239-44.
Gastroenterology 2005 Aug;129(2):415-21.

RISK FACTORS FOR COLORECTAL CANCER (COMPARISON OF RELATIVE RISKS)



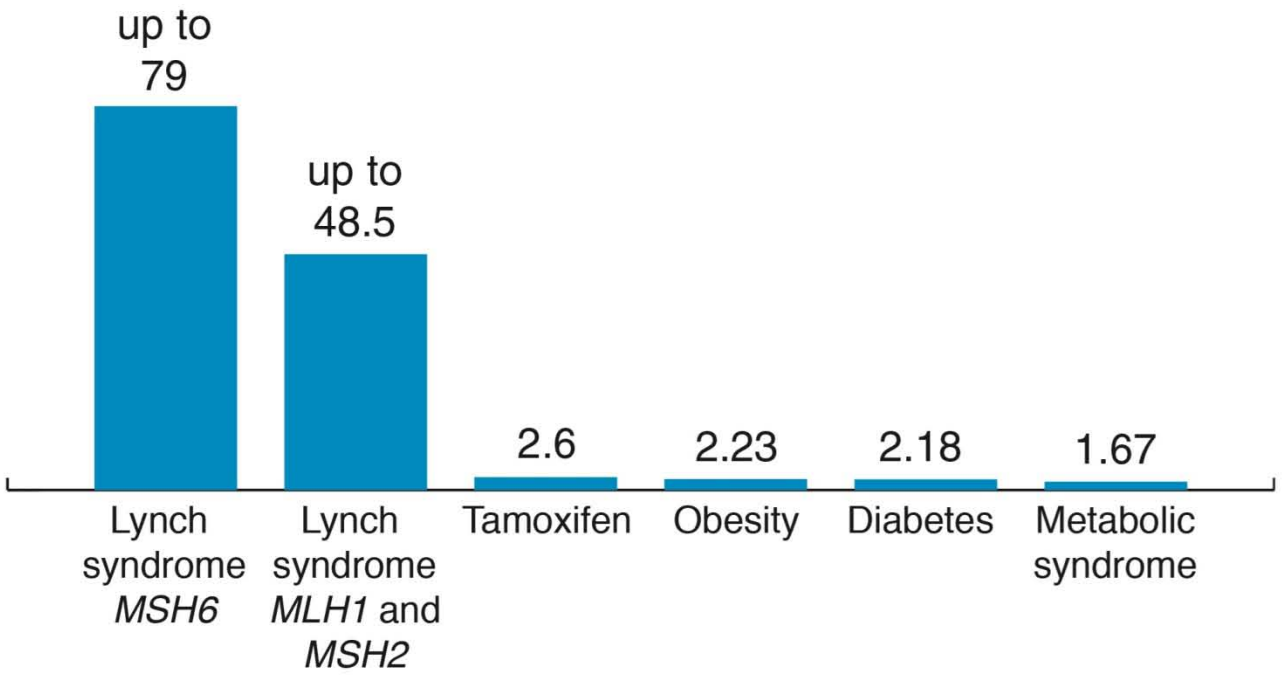
Cancer Causes Control 2000;11: 477-88.
Seer.cancer.gov/statistics/

LYNCH SYNDROME IS THE SINGLE MOST COMMON EXPLANATION FOR HEREDITARY GYNECOLOGICAL CANCERS

- ~ 2-4% of all endometrial cancer is due to Lynch syndrome
- ~9% of endometrial cancer under age 50 is due to Lynch syndrome
- Gynecologic (endometrial or ovarian) cancer is often the sentinel cancer

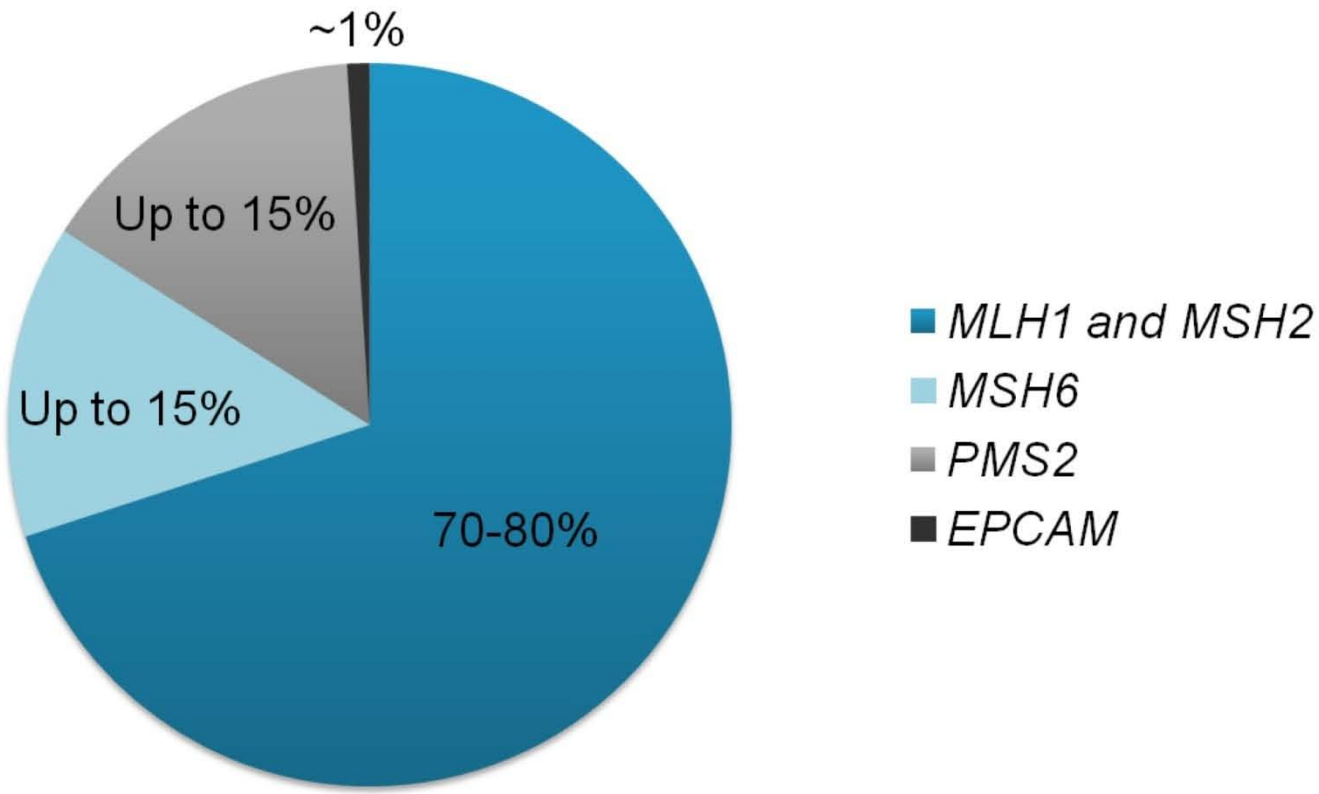
Cancer Control 2009;16:14–22 .
Journal of Clinical Oncology 2007; 25(33):5158-5164.
Obstetrics and Gynecology 2005;105:569-74.

RISK FACTORS FOR ENDOMETRIAL CANCER (COMPARISON OF ODDS RATIOS)



Ann Oncol 2010 EPUB ahead of print.
Lancet Oncol 2009;10:400-408.
Journal of Clinical Oncology 2008;25:4151-4159.

PREVALENCE OF LYNCH SYNDROME MUTATIONS BY GENE



Genet Med 2009;11:42-65.
Gastroenterology 2008;135: 419-28.
Human Mutation 2011;32:407-414.

IDENTIFYING PATIENTS AT RISK FOR LYNCH SYNDROME

SOCIETAL STANDARDS AND GUIDELINES

- ACCC- Association of Community Cancer Centers
- AMA- American Medical Association
- ASCRS- American Society of Colon and Rectal Surgeons
- AGA- American Gastroenterological Association
- ASCO- American Society of Clinical Oncology
- NCCN- National Comprehensive Cancer Network
- SSO- Society of Surgical Oncology
- SGO- Society of Gynecologic Oncologists

"RED FLAGS" FOR PATIENTS WITH A CANCER DIAGNOSIS

- Colorectal or endometrial cancer before age 50
- MSI-High Histology in a colorectal cancer under age 60:
  - Mucinous, signet ring, tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, medullary growth pattern
- Abnormal MSI/IHC tumor test result (Colorectal/ Endometrial)
- Two or more Lynch syndrome cancers* at any age
- Lynch syndrome cancer with one or more relatives with a Lynch syndrome cancer
- A previously identified Lynch syndrome mutation in the family

*Lynch syndrome cancers include: colorectal, endometrial, gastric, ovarian, ureter/renal pelvis, biliary tract, small bowel, pancreas, brain, sebaceous carcinomas

Red Flags identify patients at risk for Lynch syndrome for whom further clinical evaluation to determine appropriateness of genetic testing is warranted

Assessment criteria based on medical society guidelines. For these individual medical society guidelines, go to www.myriadpro.com/guidelines

MSI TUMOR TESTING vs MSI-HIGH HISTOLOGY

- MSI Tumor Testing
  - A PCR-based test performed on the tumor tissue. If the result is MSI-high, it's likely that the tumor was caused by mismatch repair dysfunction, which indicates a possible Lynch syndrome gene mutation
  - MSI tumor testing must be ordered specifically
- MSI-High Histology
  - Specific microscopic features of colon cancer cells that make it more likely to test MSI-high, and are therefore suggestive of Lynch syndrome
  - MSI histology features are part of the standard pathology work up of a tumor and will be found on the pathology report

"RED FLAGS" FOR PATIENTS WHO DO NOT HAVE CANCER

An individual with a family history of the following:

- Two or more relatives with a Lynch syndrome cancer,* one before the age of 50
- Three or more relatives with a Lynch syndrome cancer at any age
- A previously identified Lynch syndrome mutation in the family

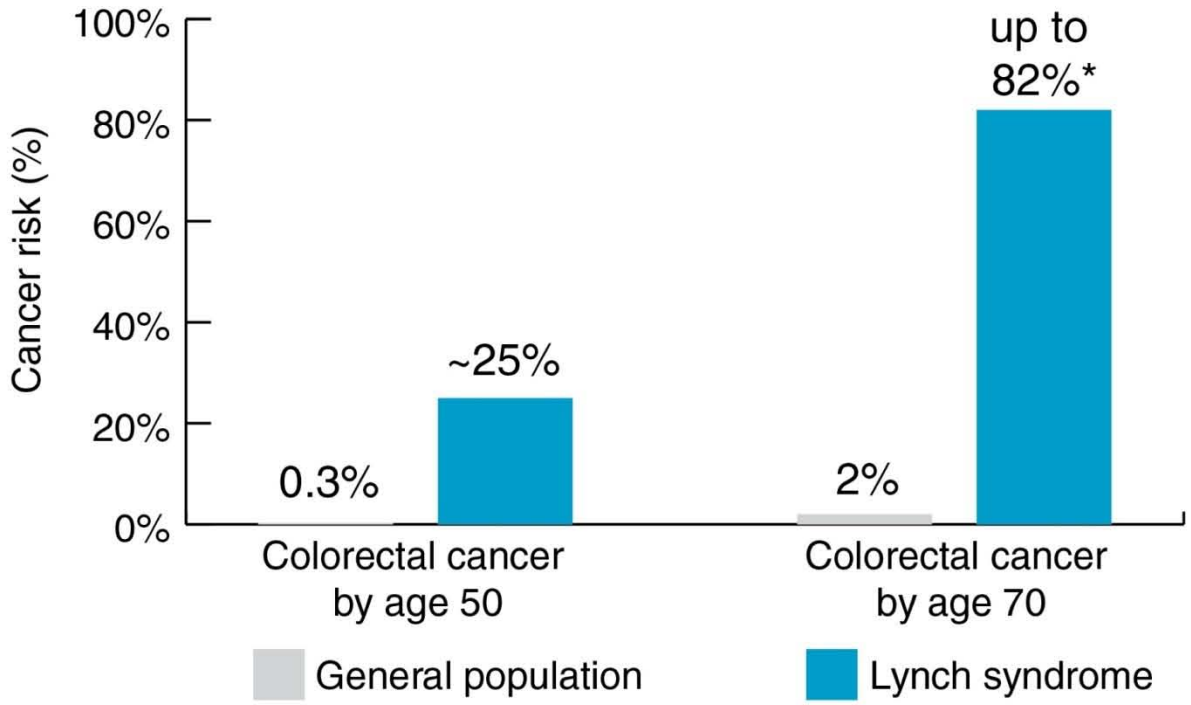
*Lynch syndrome cancers include: colorectal, endometrial, gastric, ovarian, ureter/renal pelvis, biliary tract, small bowel, pancreas, brain, sebaceous carcinomas

Red Flags identify patients at risk for Lynch syndrome for whom further clinical evaluation to determine appropriateness of genetic testing is warranted

Assessment criteria based on medical society guidelines. For these individual medical society guidelines, go to www.myriadpro.com/guidelines

CLINICAL FEATURES OF LYNCH SYNDROME

LYNCH SYNDROME INCREASES COLORECTAL CANCER RISK

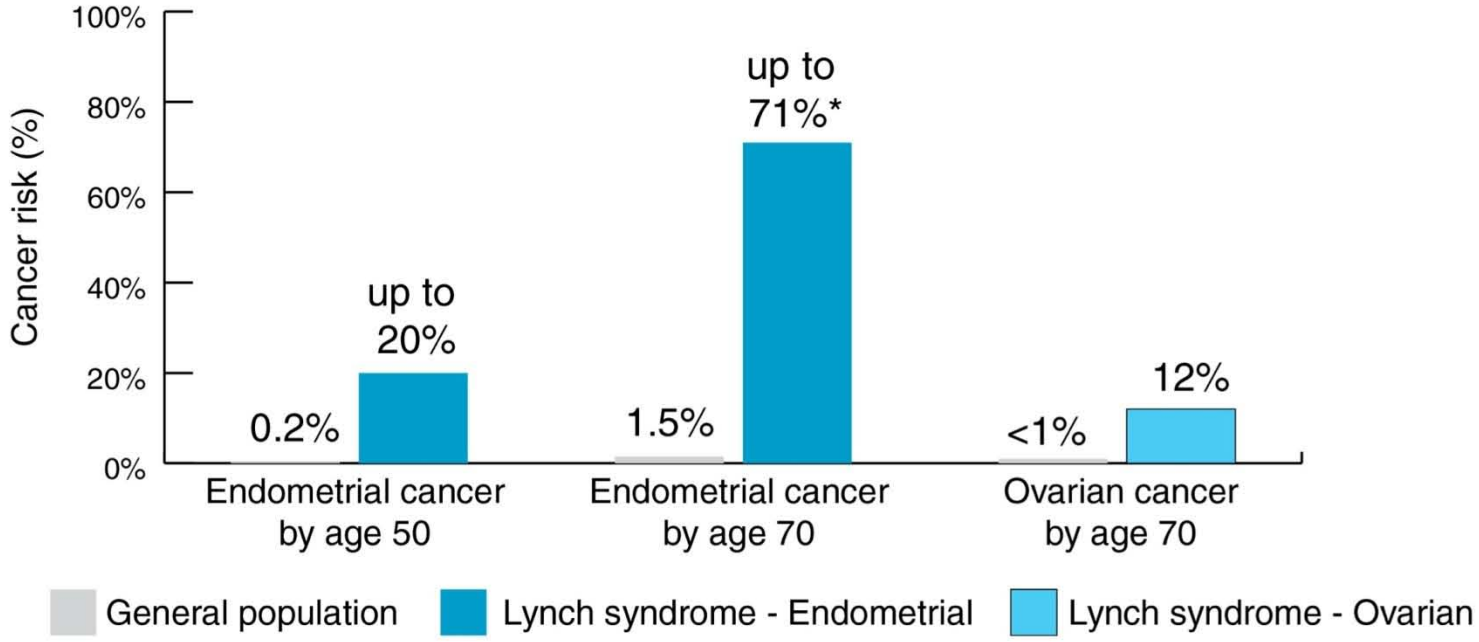


*range of risk for colorectal cancer differs by gene

Statistics in Medicine 2003;22:1837-48.
Int J Cancer 1999;81:214-8.
Gastroenterology 2009;137(5):1621–1627.
Gastroenterology 1996;110:1020-7.
Lancet Oncol 2011;12:49-55.
Gastroenterology 2008;135(2):419-28.

LYNCH SYNDROME INCREASES GYNECOLOGIC CANCER RISKS

- Women with Lynch syndrome may present with a gynecologic cancer first



*range of risk for endometrial cancer differs by gene

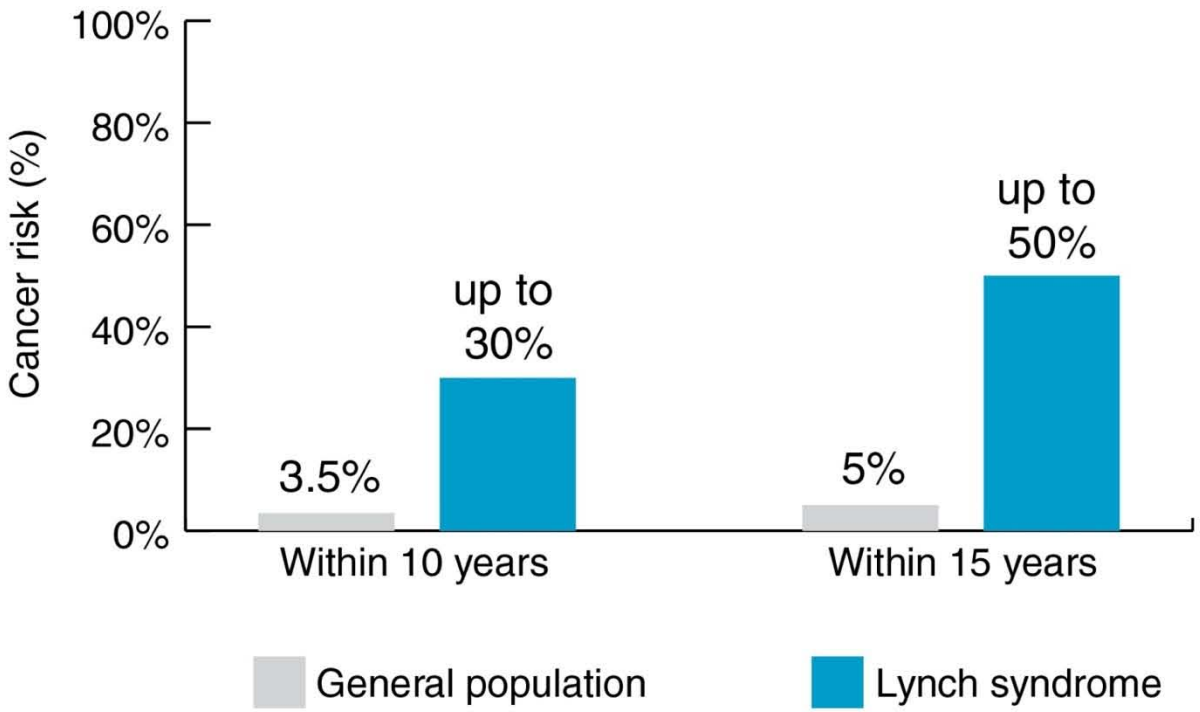
Gastroenterology 1996;110:1020-7.
Int J Cancer 1999;81:214-8.
Gastroenterology 2004;127:17-25.
Lancet Oncol 2011;12:49-55.
Gastroenterology 2009;137(5):1621–1627.
Gastroenterology 2008;135(2):419-28.

LYNCH SYNDROME INCREASES RISK FOR OTHER CANCERS

CANCER	GENERAL POPULATION RISK	RISKS IN LYNCH SYNDROME
Gastric	<1%	Up to 13%
Hepatobiliary tract	<1%	<10%
Ureter/renal pelvis	<1%	<10%
Small bowel	<1%	<5%
Brain/central nervous system (usually glioblastoma)	<1%	<5%
Pancreatic	<1%	<5%
Sebaceous adenoma or carcinoma	<1%	<10%

International Journal of Cancer 2008;123:444-449.
Clinical Genetics 2009;75:141-9.

LYNCH SYNDROME INCREASES RISK OF A SECOND CANCER



Cancer 1977;40:1849.
Dis Colon Rectum 1986;29:160.
Cancer 1993;36:388-93.

MANAGING HEREDITARY CANCER RISKS

MANAGING CANCER RISK IN LYNCH SYNDROME

- Surveillance
- Surgery

Any discussion of medical management options is for general informational purposes only and does not constitute a recommendation. While genetic testing and medical society guidelines provide important and useful information, medical management decisions should be made based on consultation between each patient and his or her healthcare provider.

Gastroenterology 2000;118:829-34.
Dis Colon Rectum 2002;45:1588-94.
JAMA 2006 Sep 27;296(12):1507-17.
www.nccn.org

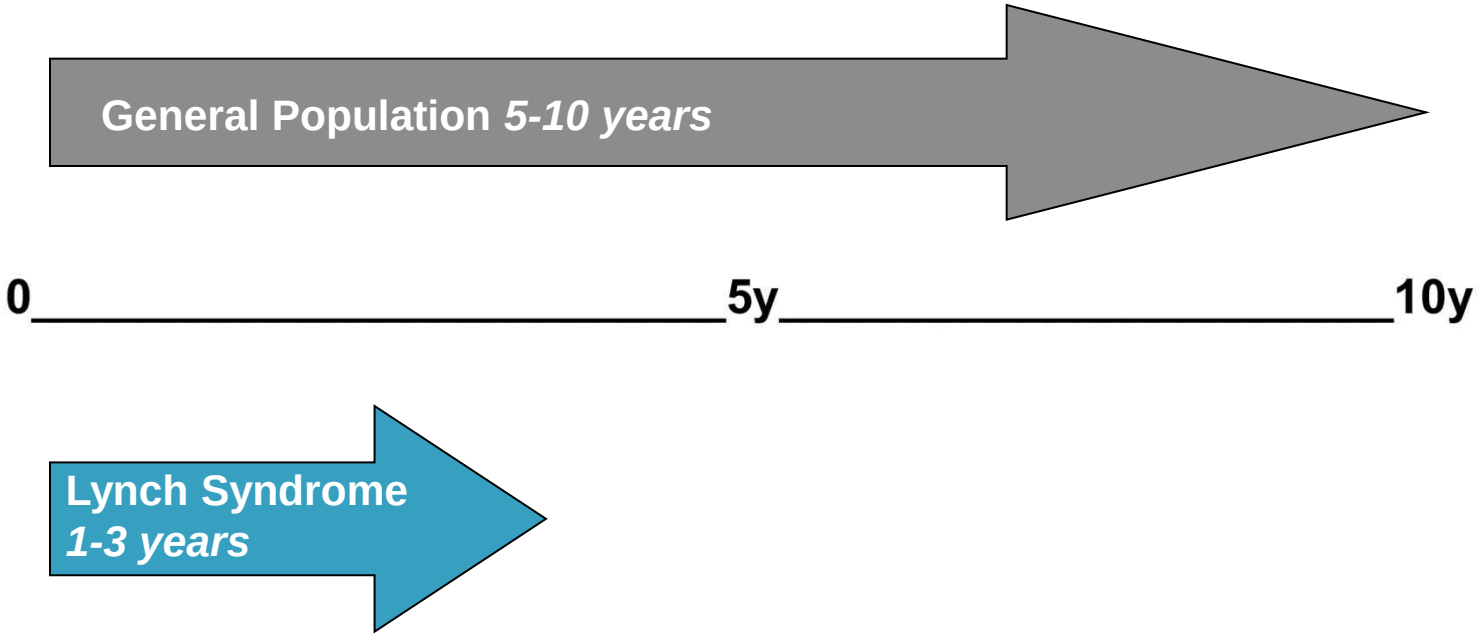
LYNCH SYNDROME
COLORECTAL CANCER SURVEILLANCE

- Colonoscopy at age 20-25y or 2-5y prior to earliest CRC under 25y, repeat every 1-2y
- Adenomas/cancers are often right-sided in Lynch syndrome
- Reduces CRC risk by over 50% and overall mortality by 65%
  - Results in diagnosis of earlier stage cancers

www.nccn.org
Gastroenterology 2000;118:829-34.
Gastroenterology 2010;138:2300-2306.
Gastroenterology 1993;104:1535-49.
Dis Colon Rectum 2002;45:1588-94.

RATIONALE FOR FREQUENT COLONOSCOPY

- Accelerated progression from adenoma to cancer



Am J Med 1999;107:68-77.
Gut 2002 Feb;50(2):228-34.
Clin Gastroenterol Hepatol 2011;9(4):340-43.

LYNCH SYNDROME COLORECTAL CANCER SURGICAL MANAGEMENT

- Surgical Considerations
  - For patients with colorectal cancer or more than one advanced adenoma consider colectomy with ileorectal anastomosis **OR**
  - Hemicolectomy with annual colonoscopy
- Surveillance options for patients with colorectal cancer
  - If hemicolectomy is performed, follow up with annual colonoscopy

Diseases of the Colon & Rectum 2003;46:1001-12.
www.nccn.org
CA Cancer J Clin 2006 May-Jun;56(3):160-7.
Annals of Surgery 2010;252:507-513.

LYNCH SYNDROME MANAGEMENT GYNECOLOGIC CANCERS

	PROCEDURE	AGE
Surveillance	*Options include:* -annual transvaginal ultrasound; -annual endometrial aspiration; -CA-125 testing	Begin at age 30-35 years
Surgical management	Hysterectomy and bilateral salpingo-oophorectomy	Option after childbearing is complete and/or at time of any intra-abdominal surgery

www.nccn.org
J Clin Oncol 2006 Oct 1;24(28):4642-60.
JAMA 2006 Sep 27;296(12):1507-17.
N Engl J Med 2006 Jan 19;354(3):261-9.

LYNCH SYNDROME MANAGEMENT OTHER CANCERS

	PROCEDURE*	AGE TO BEGIN	FREQUENCY
Gastric/small bowel cancer surveillance	Consider upper GI endoscopy *(including side-viewing examination)* Consider capsule endoscopy	30-35 years	2-3 years *(depending upon findings)*
Urothelial cancer	Consider urinalysis	Not specified	Annual
CNS cancer	Physical examination	Not specified	Annual
Pancreatic cancer	No recommendations at this time		

*Limited efficacy data

INTERPRETING AND UTILIZING TEST RESULTS IN MEDICAL MANAGEMENT

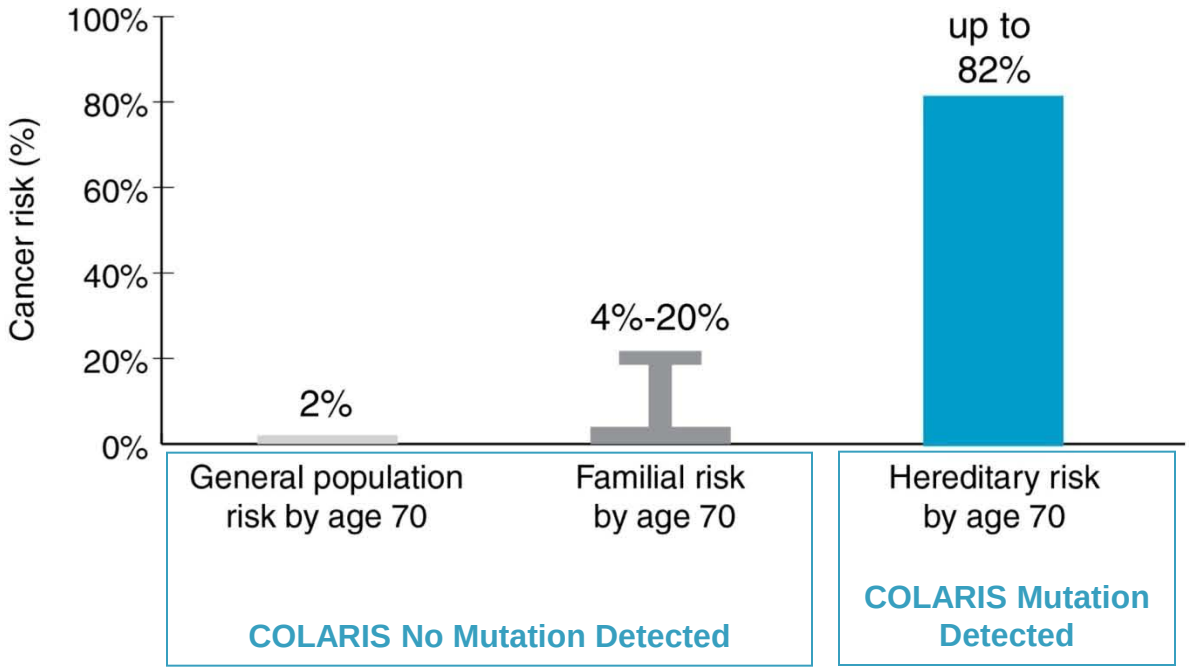
INTERPRETING GENETIC TEST RESULTS

- Positive for deleterious mutation(s) 
- No mutation detected
  - Mutation(s) previously identified in the family 
  - No known mutation in the family 
- Genetic variant of uncertain clinical significance 

POSITIVE FOR DELETERIOUS MUTATION(S)

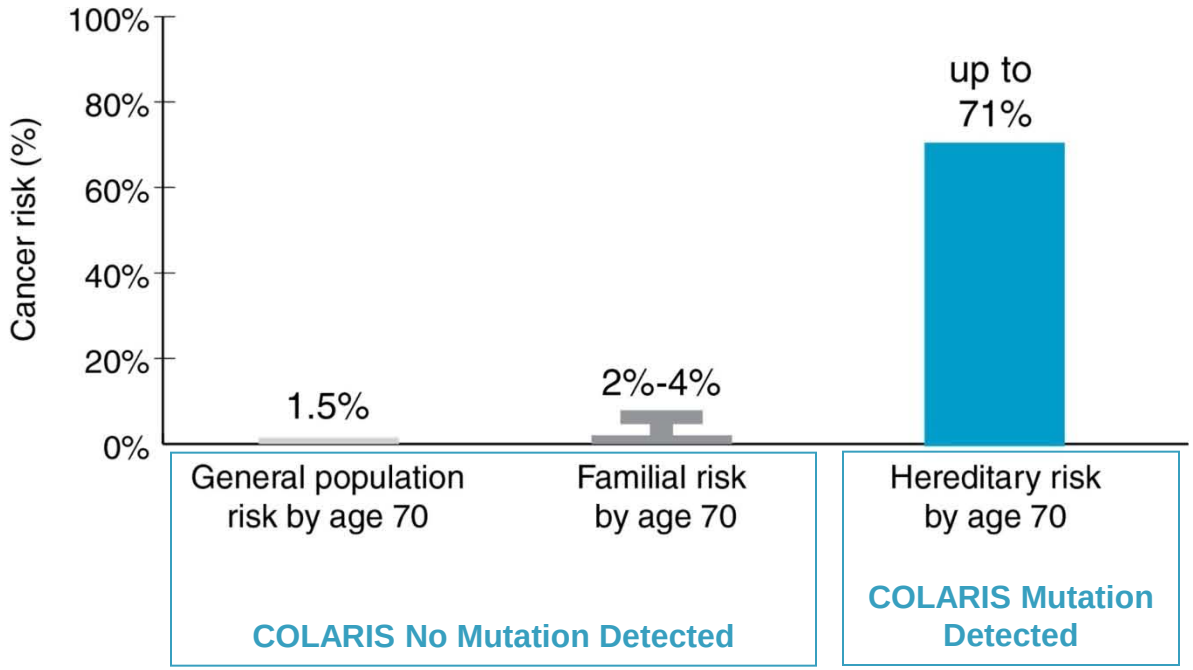
- Syndrome-associated cancer risks
- Relatives at risk
  - 50% chance for first degree relatives (children, siblings, parents) to inherit the mutation causing Lynch syndrome
- Test at-risk relatives for identified familial mutation(s)

INTERPRETING TEST RESULTS
UNAFFECTED PATIENT (COLORECTAL)



Gastroenterology 1996;110:1020-7.
Gastroenterology 2009;137(5):1621-7.
NCI (SEER) 2010.
Gastroenterology 2010;138:877-885.
European Journal of Cancer 2006;42:216-17.

INTERPRETING TEST RESULTS
UNAFFECTED PATIENT (UTERINE)



European Journal of Cancer 2005;41:2155-59.
Current Opinion in Genetics and Development 2010;20:231-38.
European Journal of Cancer 2004;40:91-95.

NCI (SEER) 2010.
Gastroenterology 2004;127:17-25.
Gastroenterology 1996;110:1020-7.

GENETIC VARIANT OF UNCERTAIN SIGNIFICANCE

- Clinical significance not yet known
- Manage based on personal & family cancer/ adenoma history
- May be further clarified by
  - Testing of specified family members
  - Molecular or functional analysis
  - Population studies

BENEFITS AND LIMITATIONS OF GENETIC TESTING

- Benefits
  - Allows for individualized medical management
  - Accurate risk assessment
  - Alleviates uncertainty and anxiety
- Limitations
  - Genetic testing does not identify all causes of hereditary colorectal cancer

IN SUMMARY

- Screen for “Red Flags”
  - Colorectal cancer before age 50
  - Endometrial cancer before age 50
  - Two or more Lynch syndrome-related cancers in an individual or family
- Discuss genetic testing options
- Interpret genetic test results and stratify risk accordingly
- Establish appropriate medical management plan

KNOWLEDGE IS POWER…
AND HOPE

SUPPLEMENTAL SLIDES

CANCER RISKS DIFFER BY GENE

GENE	MEAN AGE COLON CANCER	CRC	GYNECOLOGIC CANCER
MLH1 *MSH2*	58 years	Up to 82%	**Endometrial**: up to 60% **Ovary**: up to 12%
MSH6	54 years	**Men**: up to 69% **Women**: up to 30%	**Endometrial**: up to 71% **Ovary**: up to 12%
PMS2	50 years	**Men**: up to 20% **Women**: up to 15%	**Endometrial**: up to 15% **Ovary**: Increased, exact risk has not been defined

Gastroenterology 1996;110;1020-1027.
International Journal of Cancer 1999;81:214-218.
Gastroenterology 2004;127;17-25.
Gastroenterology 2008;135:419-428.
Lancet Oncology 2010;12:49-55.
Gastroenterology 2005 Aug;129(2):415-21.

NO MUTATION DETECTED
NO KNOWN MUTATION IN THE FAMILY

- Rules out known causes of Lynch syndrome
- Manage based on the negative result and personal & family cancer/adenoma history
- If patient was unaffected, consider testing an affected relative for Lynch syndrome (either via genetic testing or tumor analysis)

NO MUTATION DETECTED: NEGATIVE FOR KNOWN MUTATION(S) IN THE FAMILY

- General population cancer risks—if no cancer history on the other side of the family
- Avoid unnecessary screening/surgery

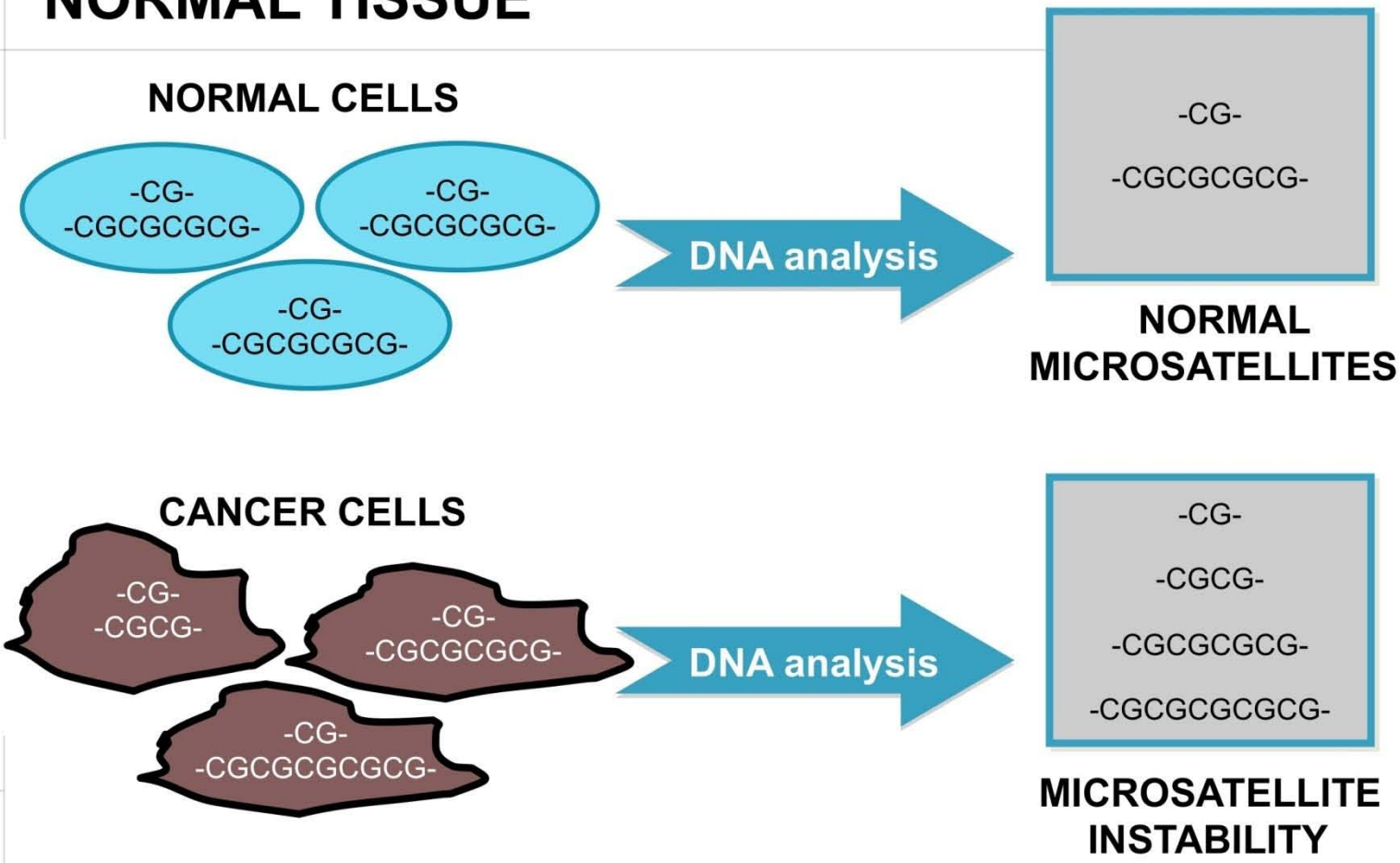
GENETIC DISCRIMINATION MYTH VERSUS REALITY

- Federal and state laws prohibit the use of genetic information as a ‘pre-existing condition’
  - Federal HIPAA legislation
  - The majority of states have additional laws
  - Genetic Information Nondiscrimination Act (GINA)

TESTING FOR HEREDITARY CANCER RISK

- Available through healthcare providers
- Federally-certified clinical laboratory
  - Turnaround time ~2 weeks
  - Insurance preauthorization services available

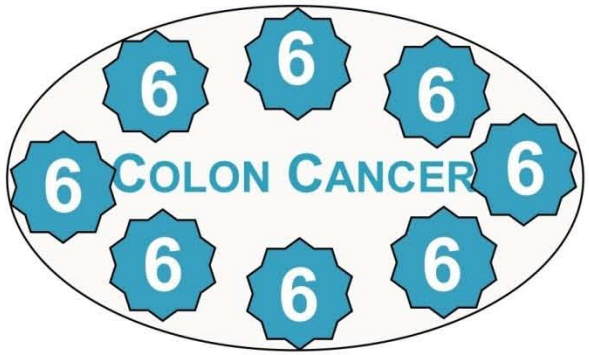
MICROSATELLITE INSTABILITY (MSI) MICROSATELLITES IN TUMOR COMPARED TO NORMAL TISSUE



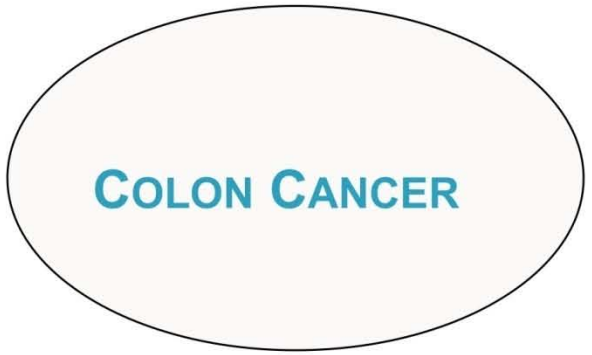
MSI analysis compares DNA extracted from slides of paraffin-embedded colorectal cancers to DNA from normal tissue

IMMUNOHISTOCHEMISTRY (IHC)

- Antibody stains look for MMR proteins: *MLH1*, *MSH2*, *MSH6* and *PMS2*
- Lack of staining = missing protein and possibility of an underlying genetic mutation



Normal expression of *MSH6* protein



MSH6 protein absent

SCREENING FOR LYNCH SYNDROME: MSI AND IHC

- MSI and IHC testing can be used as screening tools and are not diagnostic for Lynch syndrome

	SPORADIC CANCER*	LYNCH SYNDROME-RELATED CANCER*
Colorectal & Endometrial cancer	10-15%	Up to 90-95%

- Challenges in performing MSI and IHC testing, and in results interpretation exist

*MSI-H or loss of staining of ≥1 MMR protein

www.nccn.org
Journal of Clinical Oncology 2008;26:5783-88.
Genetics in Medicine 2009;11:35-43.

TUMOR TESTING STRATEGIES FOR AFFECTED PATIENTS

- If MSI and/or IHC testing is performed on a select group of patients, Lynch syndrome cases may be missed
  - The Revised Bethesda Criteria misses up to 30% of Lynch syndrome patients
- Consider routine MSI and/or IHC screening of all colorectal and endometrial cancers regardless of age at diagnosis or family history
- Proceed to genetic testing in cases where tumor results are suggestive of Lynch syndrome

www.nccn.org
Genetics in Medicine 2009;11:35-43.

GENETIC TESTING FOR UNAFFECTED PATIENTS

- Genetic testing for unaffected patients whose risk of Lynch syndrome exceeds 5% could improve health outcomes in a cost-effective manner
- $PREMM_{1,2,6}$ model can be used to further evaluate individuals meeting 'Red Flags'
  - $PREMM_{1,2,6}$ model is available at: www.dana-farber.org/premm

Cancer Prevention Research 2011;4:9-22.

DIFFERENTIAL DIAGNOSIS ADENOMATOUS POLYPOSIS SYNDROMES

CONDITION	ATTENUATED FAMILIAL ADENOMATOUS POLYPOSIS	*MYH*-ASSOCIATED POLYPOSIS
Gene:	*APC*	*MYH*
Inheritance:	Autosomal Dominant	Autosomal Recessive
Polyp Number:	Less than 100	0 - 1000
Colorectal Cancer Risk:	≥ 80% by age 70	≥ 80% by age 70

- Can present with colorectal cancer with none or a limited number of adenomas
- Similar cancer spectrum to Lynch syndrome
- MAP can present with MSI-H and MSI-L colorectal tumors

Critical Reviews In Oncology Hematology 2010.
Gastroenterology 2004;127:444-451.

DIFFERENTIAL DIAGNOSIS
FAMILIAL COLORECTAL CANCER TYPE X (FCCTX)

ETIOLOGY:	Unknown; likely heterogeneous
CLINICAL DEFINITION:	Amsterdam-1 criteria without evidence of MMR deficiency
FREQUENCY:	40-50% of families meeting the Amsterdam-1 criteria

- Increased risk of colorectal cancer only
- Lower risk of colorectal cancer compared to Lynch syndrome with a later mean age of cancer diagnosis
- Fewer right-sided, synchronous and metachronous colorectal cancers

Am J Gastroenterol 2006;101(2):385-98.

MSI-H COLORECTAL CANCER HISTOLOGY

- Right-sided
- Poorly differentiated
- Tumor infiltrating lymphocytes
- Crohn's-like lymphocytic reaction
- Mucinous
- Signet-ring differentiation
- Medullary growth pattern

Journal of the National Cancer Institute 2004;96:261-8.

ENDOMETRIAL CANCER HISTOLOGY

- Wide variety of histologic types, including endometroid and non-endometroid tumors
- Increased association between Lower Uterine Segment tumors and Lynch syndrome

Cancer 2006;106:87-94.