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.
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

Familial Cancer 2005;4:239-44.
RISK FACTORS FOR COLORECTAL CANCER (COMPARISON OF RELATIVE RISKS)

- Lynch syndrome: up to 40
- Obesity: 1.7
- Inflammatory Bowel Disease: 1.5
- Alcohol consumption: 1.2
- Red meat consumption: 1.2
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

RISK FACTORS FOR ENDOMETRIAL CANCER
(COMPARISON OF ODDS RATIOS)

- Lynch syndrome
  - MSH6: up to 79
  - MLH1 and MSH2: up to 48.5
- Tamoxifen: 2.6
- Obesity: 2.23
- Diabetes: 2.18
- Metabolic syndrome: 1.67

Reference:
Lancet Oncol 2009;10:400-408.
PREVALENCE OF LYNCH SYNDROME MUTATIONS BY GENE

- **MLH1 and MSH2**: 70-80%
- **MSH6**: Up to 15%
- **PMS2**: Up to 15%
- **EPCAM**: ~1%

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 hereditary cancer 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 hereditary cancer 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

LYNCH SYNDROME INCREASES GYNECOLOGIC CANCER RISKS

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

![Bar chart showing cancer risk for Lynch syndrome compared to general population.](chart.png)

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*range of risk for endometrial cancer differs by gene

LYNCH SYNDROME INCREASES RISK FOR OTHER CANCERS

<table>
<thead>
<tr>
<th>CANCER</th>
<th>GENERAL POPULATION RISK</th>
<th>RISKS IN LYNCH SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>&lt;1%</td>
<td>Up to 13%</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Ureter/renal pelvis</td>
<td>&lt;1%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Brain/central nervous system (usually glioblastoma)</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Sebaceous adenoma or carcinoma</td>
<td>&lt;1%</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>
LYNCH SYNDROME INCREASES RISK OF A SECOND CANCER

Cancer risk (%)

Within 10 years

Within 15 years

3.5% up to 30%

5% up to 50%

General population

Lynch syndrome

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 hereditary cancer 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.
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
RATIONALE FOR FREQUENT COLONOSCOPY

- Accelerated progression from adenoma to cancer

General Population 5-10 years

Lynch Syndrome 1-3 years

Gut 2002 Feb;50(2):228-34.
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
  - Hemicolecctomy with annual colonoscopy
- Surveillance options for patients with colorectal cancer
  - If hemicolecctomy is performed, follow up with annual colonoscopy
# Lynch Syndrome Management

## Gynecologic Cancers

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Options Include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>annual transvaginal ultrasound; annual endometrial aspiration; CA-125 testing</td>
</tr>
<tr>
<td>Surgical management</td>
<td>Hysterectomy and bilateral salpingo-oophorectomy</td>
</tr>
</tbody>
</table>

**Age**

- Begin at age 30-35 years
- Option after childbearing is complete and/or at time of any intra-abdominal surgery
# LYNCH SYNDROME MANAGEMENT

## OTHER CANCERS

<table>
<thead>
<tr>
<th>Procedure*</th>
<th>Age To Begin</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric/small bowel cancer surveillance&lt;br&gt;Consider upper GI endoscopy&lt;br&gt;Consider capsule endoscopy</td>
<td>30-35 years</td>
<td>2-3 years (depending upon findings)</td>
</tr>
<tr>
<td>Urothelial cancer&lt;br&gt;Consider urinalysis</td>
<td>Not specified</td>
<td>Annual</td>
</tr>
<tr>
<td>CNS cancer&lt;br&gt;Physical examination</td>
<td>Not specified</td>
<td>Annual</td>
</tr>
<tr>
<td>Pancreatic cancer&lt;br&gt;No recommendations at this time</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Limited efficacy data
INTERPRETING AND UTILIZING TEST RESULTS IN MEDICAL MANAGEMENT
INTERPRETING HEREDITARY CANCER 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)

- General population risk by age 70: 2%
- Familial risk by age 70: 4%-20%
- Hereditary risk by age 70: up to 82%

COLARIS No Mutation Detected
COLARIS Mutation Detected

©2012, Myriad Genetic Laboratories, Inc.
NCI (SEER) 2010.
INTERPRETING TEST RESULTS
UNAFFECTED PATIENT (UTERINE)

Cancer risk (%)

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%

General population risk by age 70
1.5%

Familial risk by age 70
2%-4%

Hereditary risk by age 70
up to 71%

COLARIS No Mutation Detected

COLARIS Mutation Detected

NCI (SEER) 2010.

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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 HEREDITARY CANCER TESTING

- Benefits
  - Allows for individualized medical management
  - Accurate risk assessment
  - Alleviates uncertainty and anxiety

- Limitations
  - Hereditary cancer 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 hereditary cancer testing options
- Interpret hereditary cancer test results and stratify risk accordingly
- Establish appropriate medical management plan
KNOWLEDGE IS POWER... AND HOPE
SUPPLEMENTAL SLIDES
# CANCER RISKS DIFFER BY GENE

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

Reference:
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 hereditary cancer 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

NORMAL CELLS

-DG-
-CGCGC-NGC-

-DG-
-CGCGC-NGC-

-DG-
-CGCGC-NGC-

DNA analysis

NORMAL MICRO SATELLITES

-CG-
-CGCGC-NGC-

-CG-
-CGCGC-NGC-

-CG-
-CGCGC-NGC-

DNA analysis

CANCER CELLS

-Microsatellite Instability

-DG-
-CGCGC-NGC-

-DG-
-CGCGC-NGC-

-DG-
-CGCGC-NGC-

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

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IMMUNOHISTOCHEMISTRY (IHC)

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

\begin{itemize}
  \item Normal expression of \textit{MSH6} protein
  \item \textit{MSH6} protein absent
\end{itemize}
SCREENING FOR LYNCH SYNDROME: MSI AND IHC

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

<table>
<thead>
<tr>
<th></th>
<th>SPORADIC CANCER*</th>
<th>LYNCH SYNDROME-RELATED CANCER*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal &amp;</td>
<td>10-15%</td>
<td>Up to 90-95%</td>
</tr>
<tr>
<td>Endometrial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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
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 hereditary cancer testing in cases where tumor results are suggestive of Lynch syndrome
HEREDITARY CANCER TESTING FOR UNAFFECTED PATIENTS

- Hereditary cancer 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
# Differential Diagnosis

## Adenomatous Polyposis Syndromes

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>Attenuated Familial Adenomatous Polyposis</th>
<th>MYH-Associated Polyposis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene:</td>
<td>APC</td>
<td>MYH</td>
</tr>
<tr>
<td>Inheritance:</td>
<td>Autosomal Dominant</td>
<td>Autosomal Recessive</td>
</tr>
<tr>
<td>Polyp Number:</td>
<td>Less than 100</td>
<td>0 - 1000</td>
</tr>
<tr>
<td>Colorectal Cancer Risk:</td>
<td>≥ 80% by age 70</td>
<td>≥ 80% by age 70</td>
</tr>
</tbody>
</table>

- 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
## DIFFERENTIAL DIAGNOSIS
### FAMILIAL COLORECTAL CANCER TYPE X (FCCTX)

<table>
<thead>
<tr>
<th>ETIOLOGY:</th>
<th>Unknown; likely heterogeneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL DEFINITION:</td>
<td>Amsterdam-1 criteria without evidence of MMR deficiency</td>
</tr>
<tr>
<td>FREQUENCY:</td>
<td>40-50% of families meeting the Amsterdam-1 criteria</td>
</tr>
</tbody>
</table>

- 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
MSI-H COLORECTAL CANCER HISTOLOGY

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

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