Genetic testing for Inherited Colorectal Cancer Syndromes

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"That's not quite the stool sample we had in mind, Mr. O'Donnell."
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: \textit{MLH1, MSH2, MSH6, PMS2, and EPCAM}
- Autosomal dominant inheritance
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 LYNCH SYNDROME

- Early onset colorectal cancer (<50y)
- Early onset endometrial cancer (<50y)
- Two or more Lynch syndrome cancers*
  - In the same individual  OR
  - Among close relatives
- 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
‘Young’ due to Cancer

Age 47 Colon Cancer Age 53 Gastric Cancer

Age 57 Prostate cancer

Age 59 Healthy Colonoscopy ‘OK’

Age 60 Small bowel carcinoma Diagnosed age 32 with cecal cancer

Age 40 Metastatic colon cancer

Age 40 Endometrial cancer

MI

Unknown

MVA
LYNCH SYNDROME INCREASES COLORECTAL CANCER RISK

*range of risk for colorectal cancer differs by gene

Age 58
Rectal Cancer

Age 78
Ovarian Cancer

Age 58
Rectal Cancer
Endometrial Cancer age 60; Colon cancer age 80

Dolph age 50 wants to know what to do?
LYNCH SYNDROME INCREASES GYNECOLOGIC CANCER RISKS

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

![Bar chart showing cancer risk percentages for endometrial and ovarian cancers in general population and Lynch syndrome patients.]

*range of risk for endometrial cancer differs by gene

Who gets missed?

- Affected
- Unknown
- Unaffected 33
- At risk

Colon cancer age 33

Colon cancer age 50

Age 32
Age 25
Sigmoid colon cancer
MSH-2 Mutation

- Subtotal colectomy
- Right transurethral resection of tumor
- Yearly endoscopy
- EGD normal
- Testing of at risk family members
Who’s Life Can You Change?
LYNCH SYNDROME INCREASES COLORECTAL CANCER RISK

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RATIONALE FOR FREQUENT COLONOSCOPY

- Accelerated progression from adenoma to cancer

General Population 5-10 years

0 .................................................. 5y ................................. 10y

Lynch Syndrome
1-3 years

Gut 2002 Feb;50(2):228-34.
2 cohorts of families of Lynch Syndrome
   ✔ 133 agreed to screening (screening cohort)
   ✔ 119 did not undergo screening (control)

Incidence of colorectal cancer
   ✔ 8/133 (6%) in screened cohort vs. 19/119 (16%)
      \[ p=0.014 \]

   ✔ Median follow-up 14.5 years

LYNCH SYNDROME INCREASES GYNECOLOGIC CANCER RISKS

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These patients must be identified and diagnosed

✓ It’s our responsibility
Table 2. The Revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability (MSI)

Tumors from individuals should be tested for MSI in the following situations:
1. Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors,* regardless of age.
3. Colorectal cancer with the MSI-H† histology‡ diagnosed in a patient who is less than 60 years of age.§
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years.
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age.
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QUESTIONS?