Genetics Corner:
Hereditary Colon Cancer Testing and Management Updates

As a health care provider, it is important to incorporate updates to national guidelines for patient management into daily practice. The following are the second version of up-dates to the 2013 National Comprehensive Cancer Network (NCCN) guidelines for colorectal cancer screening for hereditary syndromes:

Lynch Syndrome (LS) is a hereditary (non-polyposis) syndrome which is associated with strong increased risks for colon and uterine cancers, as well as increased risks for other cancers, including cancers of the ovaries, stomach, small bowel, and urinary tract. The best way to determine whether an individual has LS is to test either the patient's cancerous colon tumor or uterine tumor.

- The criteria for LS tumor testing had already included any patient who met revised Bethesda guidelines or Amsterdam criteria, individuals with endometrial cancer under 50 years of age, and individuals who have a family member with a LS mutation. Thus, previously, guidelines for tumor testing were restricted mostly to patients diagnosed with colon cancer at 50 years or younger. Now guidelines for LS tumor testing have been expanded to allow the clinician to choose from one of the two following options; perform tumor testing on all individuals diagnosed with colon cancer 70 years of age or younger, or perform tumor testing on all individuals with colon cancer regardless of their age at diagnosis.
- Previous guidelines stated genetic testing should be 'considered' for at-risk family members of a known LS mutation carrier. Now the recommendation has been re-worded to stress that genetic testing should be offered to at-risk family members.

Individuals with Lynch syndrome often have an identifiable mutation in one of the following genes; MLH1, MSH2, MSH6, or PMS2. The management for LS is now more gene-specific:
Surveillance for MLH1 and MSH2 mutation carriers:

- (The recommendation for colonoscopy beginning at age 20-25 every 1-2 years remains the same.)
- Previously, consideration of EGD with extended duodenoscopy was suggested at 2-3 year intervals. Now this screening is suggested for "selected individuals" or "families of those with Asian descent". The interval of screening is increased to every 3-5 years. The use of capsule endoscopy for small bowel cancers has been completely omitted from the current guidelines.
- There has never been clear evidence to support screening for gastric, duodenal, or small bowel cancers for people with LS.
- The possible association between breast cancer and LS has been acknowledged in the current guidelines. However, no recommendations for breast cancer risk management based due to a diagnosis of LS have been made.
- Data suggests that aspirin decreases the risk of colon cancer among patients with LS, but the data is insufficient to make a recommendation for its standard use.

Surveillance for MSH6 mutation carriers:

- Colon cancer screening guidelines suggest that colonoscopy begin at age 30-35, or possibly earlier depending of the individual's family history, and every 2-3 years thereafter.

Then every 1-2 years after age 40.

- Prophylactic hysterectomy with bilateral salpingo-oophorectomy for women who have finished childbearing should be considered (same for MLH1 and MSH2 mutation carriers).
- The risk for other cancer types is low. Due to limited data, no other screening is recommended at this time.

Surveillance for PMS2 mutation carriers:

- Colonoscopy at age 35-40, or possibly earlier depending on the individual's family history, and every 2-3 years thereafter. Then after age 50, every 1-2 years.
- The risk of other LS-related cancers is low. Due to limited data, no other screening is recommended at this time.

It is also possible for individuals with LS to have a mutation in the EPCAM gen, or to have no currently identifiable mutation. The new guidelines do not address specific management recommendations for these individuals

Familial Adenomatous Polyposis (FAP) is caused by APC gene mutations. Individuals with FAP develop 100s, if not 1000s, of colonic polyps and are nearly certain risk to develop colon cancer if untreated. There are also small increased risks for duodenal cancers, thyroid cancer, medulloblastomas, and other cancers. There is also an in-creased incidence of non-cancerous findings, such as desmoid tumors, osteomas, and supernumerary teeth.

- A desmoid tumor is a benign tumor that has the po-tential to grow large enough to inhibit the function of other tumors, and is strongly associated with Familial Adenomatous Polyposis (FAP). Now, in addition to previously recognized risk factors for hereditary cancer, any patient with a desmoid tumor meets criteria for a hereditary cancer evaluation.
- The risk for hepatoblastoma (1-2%, usually <6 years of age) and duodenal cancers (4-12%) were clarified.

Attenuated FAP (AFAP) has a similar clinical presentation as FAP, and is caused by a specific subset of mutations within the APC gene. The main difference is that there are fewer polyps seen in AFAP compared to FAP, and the risk for colon cancer is not quite as high.

- The risk for upper GI findings, thyroid, and duodenal cancer risks are similar to FAP.
- Both fundic gland and non-fundic gland polyps can occur in the stomach. Non-fundic gland polyps that have high-grade dysplasia that cannot be removed endoscopically should be referred for gastrectomy.

MUTYH-Associated Polyposis (MAP) has is also a hereditary polyposis syndrome. Generally people with MAP have fewer colon polyps that seen in FAP or AFAP, but the number of polyps can vary greatly between indi-viduals. Unlike most hereditary cancer syndromes, it is inherited in an autosomal recessive manner. Therefore, it is unusual for more than one generation to be affected. Previous guidelines were non-specific, and current guide-lines are as follows:

- Colonoscopy every 1-2 years is recommended if pol-yp burden is small.
- Colectomy with ileorectal anastomosis (preferred) or procto-colectomy with ileal pouch-anal anastomosis should be considered if polyp burden becomes too large to be managed by polypectomy alone.
- Baseline upper endoscopy at 30-35 years of age, with follow-up the same as for FAP.
- (same for FAP and AFAP) Chemoprevention is used to manage the risk of the remaining rectum post co-lectomy. There are not any approved FDA-regulated medications for this use. Research suggests that su-lindac is the most effective polyp reducing drug, but it is unclear whether this reduces the risk for cancer.

Differentiation between syndromes: A page was added showing the overlap in testing criteria for FAP, AFAP, and MAP.

- Even when FAP appears to be clearly suspected, test-ing of MAP in addition to FAP should be considered to differentiate between FAP, AFAP, MAP, and polyposis of uncertain etiology.
- Guidelines have been added for individuals who have polyposis with no known hereditary mutation. These guidelines are similar as described above, but do not include recommendations for extra-colonic findings.

The specific genetic causes for cancer syndromes continue to be discovered. As the risks for hereditary cancers become better understood, the ways to best manage these risks become further clarified. Keeping abreast with the updates to hereditary risk management is crucial when providing the best possible care to patients.

Contact Information: As always, if you have any questions or would like to refer a patient to UT Southwestern's cancer genetics team in Dallas or Fort Worth at the Moncrief Cancer Institute, please call (214)645-2563.