Summary of Presentation Series:
"Dissecting the Utility of MSI/IHC on Colon Polyps and Extra-Colonic Cancers"

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Each year, the National Society of Genetic Counselors holds an Annual Education Conference (AEC) that serves as a way to keep those in the field of clinical genetics informed of the most recent advancements in the field of clinical genetics. The AEC invites speakers from diverse fields, including cancer, prenatal, and pediatrics to present. Below are summaries of four presentations presented in a series entitled Dissecting the Utility of MSI/IHC on Colon Polyps and Extra-Colonic Cancers.

Before getting to the summaries, I wanted to briefly review some basics about Lynch syndrome (LS). As you are aware, LS is the most common hereditary form of colon cancer and is the cause of about 2-5% of all colon cancers. People who have LS have defective mismatch repair proteins, which cause an accumulation of DNA errors. Tumor testing is the best first step to take when determining whether an individual has LS. Tumor testing can involve either immunohistochemistry staining (IHC) for mismatch repair proteins or microsatellite instability (MSI) testing for specific DNA errors. Traditionally, colon cancers are the tumor of choice for LS testing.

DNA Mismatch Repair Deficiency in Colorectal Polyps Associated with Lynch Syndrome (LS)
Elena Stoffel, MD, MPH -Division of Gastroenterology with the University of Michigan Health System

In addition to using colon cancer tumors for testing, for the past few years researchers and clinicians have been performing IHC and MSI tests on colon polyps in an attempt to diagnose LS before cancer occurs. However, the clinical utility of performing these tests on colon polyps has not been well understood. IHC and MSI testing on polyps are able to detect about 50-100% of all LS. IHC and/or MSI testing works better on adenomas that are large and/or have high grade dysplasia. Smaller, better-differentiated adenomas are more likely to give a false negative result. There is still insufficient data to determine exactly how well polyp testing works overall. It is generally believed that if IHC or MSI testing results are positive for LS, this is likely an indication that the patient has LS. However, if polyp testing is negative, LS cannot yet be ruled out.

Tissue Testing for LS: Endometrial Carcinoma (EC)
Russell Broaddus, MD, Ph.D. -Department of Pathology at MD Anderson Center

- LS-related EC is more likely to occur in the lower uterine segment of the uterus than sporadic EC.
- When testing an EC tumor for LS, it is a good idea to run both IHC and MSI, although it may be appropriate to only run IHC if the pathologist is very experienced. Using IHC alone misses about 12% of cases.
- If a patient has two LS-related cancers and testing of the first tumor is normal, it is still necessary to test the second cancer for IHC and/or MSI.
- Generally, the younger the age at cancer diagnosis, the more likely it is to be hereditary. However, sporadic EC is more likely to be diagnosed at younger ages than other cancer types. Therefore, a young age at EC diagnosis may not necessarily increase a patient¡|s risk of having LS.

- Testing of complex atypical hyperplasia can be done if EC tissue is not available. Positive tumor testing of complex atypical hyperplasia of the uterus may mean the patient has LS. However, LS cannot be ruled out if IHC and/or MSI of complex atypical hyperplasia are normal.
- In the future, tumor testing of all patients with EC or colon cancer (regardless of age) may be the norm.

Ovarian Tumors and LS
Sarah E. Kerr, MD- Senior Associate Consultant with the Mayo Clinic

- The risk for ovarian cancer among females with LS ranges from about 4-12%. Women with the highest risks and who are diagnosed at the youngest ages have MSH2 mutations.
- Although more research is needed, it appears that the histology of LS-related ovarian cancer does not differ significantly from non-LS ovarian cancer. Therefore, reviewing pathology to determine the type of ovarian cancer a patient has had may not be helpful in assessing her risk to have LS.
- Even though endometriod and clear cell tumors are types of ovarian cancers, their tissues originate from the uterus during embryonic development. Therefore, these tissues may look very similar under a microscope, and when cancer is found in the ovaries it can difficult to determine whether it represents a separate primary or whether it has spread from the uterus. If a patient has synchronous ovarian and endometrial cancers, her risk to have LS is increased. The inability to identify a cancer¡|s true origin could result in the inaccurate diagnosis of a ¡¥second primary¡|. A patient who has been told she has two primaries when she has only one will be given a falsely high risk estimate for LS.
- Unlike uterine and colon cancer, tumor testing for ovarian cancer is not well understood. Further research is needed to clarify the sensitivities and specificities of IHC and MSI testing on ovarian tumors.

Screening for Muir-Torre Syndrome using Mismatch Repair Protein Immunohistochemistry of Sebaceous Neoplasms
Megan Roberts, MS, CGC- Instructor of Medical Genetics with the Mayo Clinic

- About 9% of patients with LS have the Muir-Torre Syndrome (MTS) variation. In addition to having LS, patients with the MTS variation develop sebaceous tumors including sebaceous neoplasms. Sebaceous tumors are slow-growing papules that are yellow, pink, or flesh-colored. Of the five genes associated with LS, patients with MTS are more likely to have mutations in MSH2, followed by MLH1 and MSH6. According to Ms. Roberts, no mutations were reported in PMS2 or EPCAM.
- Researchers at the Mayo Clinic have been attempting to perform IHC staining on sebaceous neoplasms. It appears that a positive IHC staining on sebaceous neoplasms is likely a true positive, but further testing would be needed to confirm a diagnosis of MTS. A negative IHC result would be helpful in ruling out MTS. However, if available colon and/or endometrial tissues should be used instead as these appear to be much more reliable.
- Interestingly, these researchers also found that 2 out of 90 patients with sebaceous neoplasms had MYH-associated polyposis (MAP). MAP is a separate hereditary cancer syndrome that

leads to an increased risk for colon and duodenal cancers, as well as increased risk for colon polyps and benign extra-colonic findings, such as osteomas and extra teeth. There are nine other patients reported in the literature with sebaceous neoplasms who also had MAP.

- Patients who receive organ transplants are more likely to develop sebaceous neoplasms. Of patients who have received organ transplants and later develop sebaceous neoplasms, little is known about how to distinguish patients with MTS from those who do not have MTS. In a small study at the Mayo Clinic (n=24) involving patients who had sebaceous neoplasms after receiving organ transplants, they found that those with MTS developed sebaceous neoplasms much sooner (about 2 years) than non-MTS patients (about 7-8 years). Additionally, whereas non-MTS patients developed on average about 1 sebaceous neoplasm, patients with MTS were found to have on average between 15 and 18 sebaceous neoplasms.

Colon cancer testing by IHC and/or MSI remains the best first step to take when attempting to diagnose LS. However, this method can only be applied to patients who have been recently diagnosed with colon cancer. Researchers are learning more about the utility of IHC and MSI testing for extra-colonic tumors and colon polyps. Researchers also continue to look for other clues to identify sporadic cancers from LS-related cancers. The ability to diagnose LS by a variety of different well-studied testing methods will allow for an earlier and more accurate diagnosis of LS, which is the first step in reducing the risk of LS-related cancers.

As always, if you have any questions or are interested in scheduling, do not hesitate to contact our genetic counseling team at 214-645-2563.