Genetics in Your Practice

NCCN Guideline Updates
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The National Comprehensive Cancer Network has recently revised both their Breast and Ovarian Genetic/Familial High-Risk Assessment recommendations and their Colorectal Cancer Screening guidelines. We'd like to take this opportunity to highlight some of the recent changes that will potentially affect clinical practice.

The most exciting change (from our Genetics corner) is that the NCCN now defines comprehensive genetic testing to include large genomic rearrangements. Previously, the guidelines noted that large genomic rearrangements are not detectable by primary sequencing, but did not specify that additional testing (i.e. BART) should be included as part of comprehensive testing. According to laboratory data, large genomic rearrangements account for 6-10% of *BRCA1* and *BRCA2* mutations. In individuals of Latin American/Caribbean and Near East/Middle East descent, these rearrangements account for approximately 20% of mutations.

In response to this change, Myriad Genetic Laboratories has issued a statement that they will be working with insurance payers to cover the cost of BART testing, and that they anticipate broader insurance coverage in the future. However, BART must still be ordered as a separate test, and may or may not be covered by insurance. Myriad will continue to perform BART testing at no additional charge for very high risk patients (defined by their criteria or a BRCAPRO score >30%), and they will offer BART on a go forward basis to anyone who qualifies for testing via their financial assistance program. The laboratory is offering to hold samples for BART testing for all other patients until December of 2012 or until insurance coverage applies. Our group has been in the practice of offering BART as a reflex test to all patients. In our experience, most patients decline BART testing due to lack of insurance coverage. We are excited about the prospect of greater insurance coverage, which will allow more comprehensive testing for patients.

Some of the other changes to the Breast and Ovarian guidelines include: changing the recommendation for beginning CA-125 screening from age 35 to 30 (or 5-10 years before the earliest age of ovarian cancer in the family); and adding macrocephaly to the list of criteria for breast cancer patients that may warrant additional genetic risk evaluation.

In addition to the hereditary breast and ovarian cancer changes, the revised NCCN Guidelines also include several changes that pertain to Lynch syndrome management. One important change was a recommendation that infrastructure needs to be in place to handle the screening results when implementing universal IHC/MSI testing. Over the last 8 months, our group has been working with UT Southwestern and community hospitals to implement universal IHC testing at clinic sites in Dallas, Tarrant, and outlying counties. As part of this effort, we have implemented a navigation program to facilitate referrals for abnormal IHC results from the universal IHC testing program. Our two genetic navigators use a patient tracking database to ensure that patients with abnormal results have appropriate referrals. To date, we have over 1,000 patients in our navigation system, and have seen the importance of this infrastructure when dealing with a large volume of patients.

In addition to recommending implementation of infrastructure for handling universal IHC results, the guidelines also changed their recommendations for follow up of abnormal IHC results. They originally stated that abnormal IHC results should prompt "genetic testing of peripheral blood DNA to find a disease causing mutation of one of the MMR genes". The revised guideline recommends that "individuals with abnormal IHC or MSI results should preferably be referred for genetic counseling so that the appropriate follow up testing can be offered to the patient". This change highlights the complexity of interpreting IHC or MSI results, and that other tests, such as BRAF and MLH1 hypermethylation studies might be indicated in addition to germline MMR testing. It is also important to remember that IHC results should always be considered in the context of family history, and further genetic risk evaluation may be indicated for some patients with normal IHC results.

Several other changes were made in the guidelines for Lynch syndrome management:

1. The guidelines specify that patients should be educated that dysfunctional uterine bleeding warrants evaluation.
2. Recommendations for considering gastric biopsy and enteroscopy were deleted, and a comment was added that there is no clear evidence to support screening for gastric and small bowel cancer.
3. The guidelines specify that annual urinalysis should be considered starting at *age 25-30*.
4. The guidelines also specify annual physical examination starting at age 25-30 to evaluate for CNS cancers.
5. The Lynch related cancer risks were updated:

Cancer type	Risks reported in NCCN guidelines
Colon	52-82%
Endometrium	25-60%
Stomach	6-13%
Ovary	4-12%
Hepatobiliary tract	1.4-4%
Urinary tract	1-4%
Small bowel	3-6%
Brain/CNS	1-3%
Sebaceous neoplasms	1-9%
Pancreas	1-6%

It is important to remember that the risks for cancer vary depending upon gender and the causative gene. While these numbers are useful in general for counseling patients about the types of cancers associated with Lynch syndrome and their relative risks, we tailor the risks reported to our Lynch syndrome patients based on their mutation, with consideration to their personal risk factors and family history.

Our genetic counselors are always happy to discuss complex cases and other genetics-related questions. Please contact us at 817-838-4871 if we can be of assistance.