Inherited Cancer Syndromes in My Practice?

Have you ever diagnosed someone with hereditary nonpolyposis colorectal cancer (HNPCC)? Most likely not. Do you have any patients at risk for HNPCC in your practice? No? Not sure? For most providers the answer is yes – probably more than one. The disconnect between our perception of the prevalence of this disorder and the actual number of patients who are affected does our patients a disservice. Recognizing those at risk could truly save their lives.

HNPCC is likely the most common hereditary cancer syndrome, and causes about one in twenty cases of colorectal cancer (CRC). By my own admittedly "back of the envelope" estimate, the average primary care provider with a panel of 2500 patients likely cares for 3 patients carrying a genetic change causing HNPCC. The mutation confers an approximately 80% lifetime risk of developing CRC; emerging data suggest that men who are mutation carriers for HNPCC may be at higher risk of CRC than women. Often overlooked is that the mutation also contributes to the risk of developing other cancers, including an approximate 30-60% lifetime risk in women of endometrial cancer. In individuals affected by HNPCC, cancers tend to occur earlier than sporadic cancers (under the age of 50 in many cases) but not as early as the cancers seen in the much rarer and more dramatic familial adenomatous polyposis (FAP). Though inherited in an autosomal dominant pattern (50% of an affected person's offspring will inherit the disorder) the clinical presentation of HNPCC-associated CRC is often subtle, with few patients having any outward manifestation of the disorder. Frequently, the lesions are right sided, so sigmoidoscopy is not an effective detection method. On colonoscopy affected individuals often have normal or near normal numbers of polyps, rather than the hundreds to thousands seen in FAP.

There is fair evidence suggesting that early intervention (starting in the patient's 20's) with frequent colonoscopy (every one to two years) can save lives in mutation carriers. Early endometrial cancer screening is also a consideration for these patients, though clear evidence of benefit is lacking. For those with CRC and HNPCC, subtotal colectomy is a consideration. At this time, there are no data to support the use of genetic testing on a screening basis in unselected populations. How then can you identify individuals with HNPCC? One of the best approaches is to learn about your patient's family history. Formal guidelines such as the Bethesda and Amsterdam criteria can help to identify those families at high risk for HNPCC. However, these guidelines were developed for research purposes and are cumbersome for use in primary care. Red flags that might prompt a PCP to think about HNPCC include the presence of: 1) early onset CRC or endometrial cancers in the patient and/or the patient's first degree relatives; 2) multiple adenomatous polyps and or adenomatous polyps occurring at an early age in the patient and/or the patient's first degree relatives; 3) individuals with metachronous CRC; 4) individuals with multiple cancers (for example both colon and endometrial cancer in the same person); and 5) individuals whose family histories have multiple individuals with HNPCC associated cancers (CRC, endometrial, ovarian, upper urinary tract, stomach, biliary tract, brain, small intestine). For more detail see: http://www.cancer.gov/cancertopics/pdq/genetics/colorectal/HealthProfessional/page4
I f you suspect a case of HNPCC, early involvement of a specialist (e.g., a geneticist, gastroenterologist or surgeon) will probably benefit you and the patient. The decision to

obtain genetic testing for an individual thought to be at risk for HNPCC is complex, and testing should only be done after obtaining informed consent from the patient. In itself, this is

reason to involve a specialist. Complicating matters further is the fact that there are now four known genes (hMLH1, hMSH2, hMSH6, and PMS2) that can cause HNPCC if mutated. Testing can involve protein based assays and/or gene-based assays. Literally hundreds of mutations have been identified in each of these genes and, occasionally, gene alterations are turned up that have never been clearly associated with disease. This makes the results of HNPCC testing a bit more of a challenge to sort through than the average blood glucose. Finally, management options for affected patients are evolving as data on HNPCC is amassed. This makes it hard for a primary care provider to keep up with the latest advances relevant - and very important - to a small subset of their patient population.

Complicated? Yes. Does every PCP need to plumb the full depths of knowledge about HNPCC? Most certainly not. The first step is something we are all familiar with – taking a family history - armed with the knowledge that patients with HNPCC really are in your practice … and maybe in your waiting room right now.