Surgeons Have Critical Role in Genetic Testing Decisions, Medical, Legal Experts Say

What role should surgeons play in the rapidly evolving field of genetic testing for cancer? Medical and legal experts told participants in the American College of Surgeons’ spring meeting in Baltimore that surgeons should have an active, inquisitive role that focuses on the patient’s family history.

In addition to identifying a possible hereditary component to cancer in a patient and his or her family, the surgeon must decide whether there is an appropriate referral to be made to specialists for genetic testing, as well as how to manage the disease, according to Gloria Petersen, Ph.D., a genetics epidemiologist at the Johns Hopkins University, Baltimore.

Asking Questions

The key is asking detailed questions about family history that go back at least three generations and include all members of the family and their age at diagnosis, among other factors, she said. Families with individuals who have multiple primary cancers or early onset cancers, and clusters of rare or unusual cancers in a family are all flags that indicate the need for a further work-up.

Henry Greely, J.D., law professor at Stanford University, Palo Alto, Calif., told the surgeons that their role is to examine critically the need for genetic testing. A skilled and knowledgeable provider or genetic counselor is required for counseling the patient because every genetic test for every patient raises a unique set of issues that the patient must understand, he said.

“A true, informed consent process is essential,” Greely said. It should be lengthy, detailed, and go beyond the medical risks of the test, and into the social, familial, and possible psychological consequences of the test.

In the last 5 years, there have been an enormous number of discoveries, including more than three dozen cancer syndromes for which the gene has been identified, localized, or even cloned and moved into clinical practice, Petersen noted.

The current state of clinical cancer genetics is focused on improving cancer risk assessments; developing consensus on hereditary syndrome diagnoses; expanding genetic counseling services for genetic testing; using surgical methods, such as prophylactic surgery, and decision making points to manage patients with inherited cancer; and involving genetically high-risk individuals in cancer prevention, she said.

While genetic tests can have positive impacts on health by eliminating subsequent medical or surgical interventions, promoting psychological well-being, and helping people plan their lives better, there are also disadvantages, according to Greely. People who test negative may forgo future prevention and screening measures; those who test positive may suffer adverse psychological effects and disruption of family relationships as patients wonder whether their spouses will stay with them and what effect the information will have on their siblings or children. Social issues may include potential discrimination in insurance, employment, or adoption proceedings, or the fear of discrimination, he said.

Each disease has different medical and social implications and the number of people who will get the disease will vary dramatically, Greely said. He recommended that surgeons find out what types of treatments are available, how sensitive and accurate the genetic tests are, how much tests cost, and what the tests indicate about the disease risks to family members. He also suggested that surgeons talk to each patient about personal circumstances and personality.

In a cancer genetics risk assessment clinic one is likely to find an oncologist in charge of a team that includes a nurse counselor, specialists in different cancer syndromes, and ethicists. Genetic testing laboratories are likely to be on site, Petersen added. “The field is rapidly changing, and one where even the risk assessments are changing . . . and one that really requires a multidisciplinary approach,” she said.

Recognizing Familial Cancers

Bert Vogelstein, M.D., of the Johns Hopkins University, Baltimore, said that surgeons have a critical role in recognizing familial forms of cancer that may put others besides the patient at risk.
"Too many times in the clinic we see patients who are operated on for late-stage disease who tell us they had a father or a brother or some other close relative who also had colon cancer. If that information had been provided to the patient's physician long before, appropriate surveillance mechanisms could have been in place to perhaps detect that cancer earlier, perhaps even at the benign stage, and prevent the need for surgery," he said.

Colon cancer is the third most frequently diagnosed cancer. Of the 130,000 new cases diagnosed annually, about 80% are not associated with any hereditary factors that have yet been identified, and thus presumably result exclusively from mutations acquired after birth, according to Vogelstein. Of the 20% that are inherited, at least three different syndromes that now can be delineated at the clinical level illustrate the importance of preventing both tumor initiation and tumor progression, he suggested.

**Inherited Syndromes**

One syndrome, familial adenomatous polyposis (FAP), is a relatively rare condition that results in a high penetrance of disease — patients inherit a 90% likelihood of getting colon cancer in their lifetimes. In FAP, thousands of polyps are distributed throughout the colon and rectum, some of which progress to malignancy as a result of a mutation of a typical tumor suppressor gene, which causes the syndrome.

The second syndrome, hereditary non-polyposis colon cancer (HNPCC), also known as Lynch Syndrome, carries an intermediate risk and results in a lower but still significant penetrance. Individuals affected have a 30% to 70% lifetime incidence of colon cancer.

In this rare form of cancer, accounting for 1% to 3% of cases, patients have just a single polyp. The only clinical way to diagnose HNPCC, which is due to defects in DNA repair, is on the basis of family history, he said.

Familial colorectal cancer, the third syndrome, which predisposes affected individuals to a 10% to 20% lifetime incidence level, is common but is the more difficult to study and define. One cause of it, found in Vogelstein's lab, is a gene mutation common in Ashkenazi Jews and similar to the mutation in the gene for FAP.

In both FAP and HNPCC the median age of cancer development is 42.

**Prevention Targets**

Even though they are distinct in terms of their molecular biology, with FAP as a disease of tumor initiation and HNPCC as a disease of tumor progression, both stages of the disease process are important targets for prevention, Vogelstein said.

Subtle mutations in cancer genes can cause a modest but still significant increased risk of cancer, and surgeons will want to know if a patient's family members are at such an increased risk based on those inherited factors, according to Vogelstein.

While clinical diagnosis for polyposis is clear, only genetic testing can determine whether siblings also inherited the same mutations, he said. Whoever does not have the mutation can immediately know, without further colonoscopies and medical examinations, that they have no higher risk for colon cancer than the general population. Physicians then can focus on the people who do have the mutations, he said.

— Gwen Moulton

### Changes at FDA May Speed Drug Approval Process and Increase Off-Label Use

The U.S. Food and Drug Administration is developing new regulations to streamline the process of getting pharmaceuticals to market and to expand potential uses of those already available.

Revisions required by the Food and Drug Administration Modernization Act of 1997, signed into law in November 1997, have been in the works for several years. The new law requires the FDA to draft 42 new regulations, which cover wide-ranging areas of the agency's responsibilities including information about off-label drug use, pediatric use of prescription drugs, and new approval requirements for diagnostic radiopharmaceuticals. These and other changes have important implications for physicians and patients.

### Off-Label Drug Use

Most oncologists prescribe medication off-label, according to a study last year by the American Enterprise Institute and the American Cancer Society (see *News*, Aug. 20, 1997). One reason the study found that oncologists prescribe off-label is because they feel that the official labeling included in the