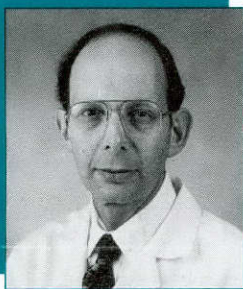


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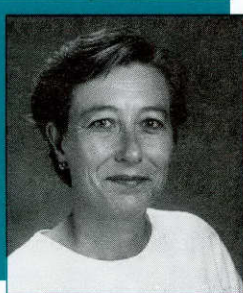
Fecal occult blood test is useful first step

M. D. Anderson researchers stress importance of annual colorectal cancer screening

Cancer Detection



Bernard Levin is vice president for cancer prevention



Constance Johnson is a senior research nurse in the Office of the Vice President for Cancer Prevention

While many people have regular mammograms and prostate cancer tests, few are screened for colorectal cancer, despite its frequency. "Colorectal cancer is very common," said Bernard Levin, M.D., vice president for cancer prevention at M. D. Anderson Cancer Center. "In the United States, there is an overall lifetime risk of about 6%, or 1 in 16. There are 138,000 new cases every year, and about 56,000 deaths." That makes colorectal cancer the second most common cause of death from cancer in the United States. And although the overall 5-year survival rate for patients with colorectal cancer is not as good as one would like (about 52%), the survival rate for those with early-stage disease is close to 100%. It is therefore imperative to identify people with colorectal cancer as early as possible.

Levin and other physicians and researchers at M. D. Anderson Cancer Center therefore strongly recommend annual colorectal cancer screening for the general population beginning at age 50. The screening tests commonly used to detect colorectal cancer in asymptomatic individuals are the digital rectal examination, the fecal occult blood test (FOBT), and flexible sigmoidoscopy. The double-contrast barium enema and colonoscopy may also be used.

Fecal occult blood test is recommended

The FOBT, although not a specific test for cancer, tests for hidden blood in the stool, a sign of colorectal cancer. Reports on the test's sensitivity and specificity have been variable, but researchers at the University of Minnesota reported a test sensitivity of 80% when the test was repeated annually over 13 years. The FOBT is most

effective when used annually for many years, said Levin, rather than as a one-time test.

The FOBT is an easy way for primary care physicians to screen for early colon cancer. And it's inexpensive: it costs only about \$10.

"The actual test itself is not that sophisticated," said Levin. Nearly all FOBTs test for the presence of blood or blood by-products in stool samples. There are two main types of tests. The immunochemical tests specifically detect human hemoglobin in the stool. "Immunochemical tests will most likely replace the guaiac-based tests," predicted Levin. The guaiac-based tests, which are simpler and more commonly used, involve guaiac-impregnated paper that when treated with hydrogen peroxidase turns blue in the presence of peroxidase-like activity in the stool. Unfortunately, because the test is not specific for hemoglobin, some vegetables with peroxidase-like activity and some foods that contain heme (such as meat) cause false positives in guaiac-based FOBTs. Patients must avoid eating those things before taking the tests.

False positives can also occur because some medical conditions other than colorectal cancer and some medications cause low but detectable levels of blood loss. One example is the gastrointestinal bleeding associated with regular aspirin use; thus, aspirin also must be avoided before stool sample collection for the FOBT.

Study reveals patient reluctance

The guaiac-based tests have been used for more than 20 years, with some modifications. In a recent report submitted for publication, Levin, Kenneth Hess, Ph.D., of the M. D. Anderson Department of Biomathematics, and Constance

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Levin and his colleagues are about to begin a national program to inform the public of the importance of testing for colorectal cancer.

M. Johnson, B.S.N., of the Division of Cancer Prevention compared three FOBTs: the nonhydrated Hemoccult® FOBT and two modified versions, the rehydrated Hemoccult® and the Hemoccult® Sensa®. In the rehydrated test, a drop of water is added to rehydrate the stool sample. This step has been shown to increase the number of positive tests, but mostly by increasing the number of false positives. The Hemoccult® Sensa® is more sensitive than the standard Hemoccult® because it contains a color enhancer that intensifies the color of a positive test.

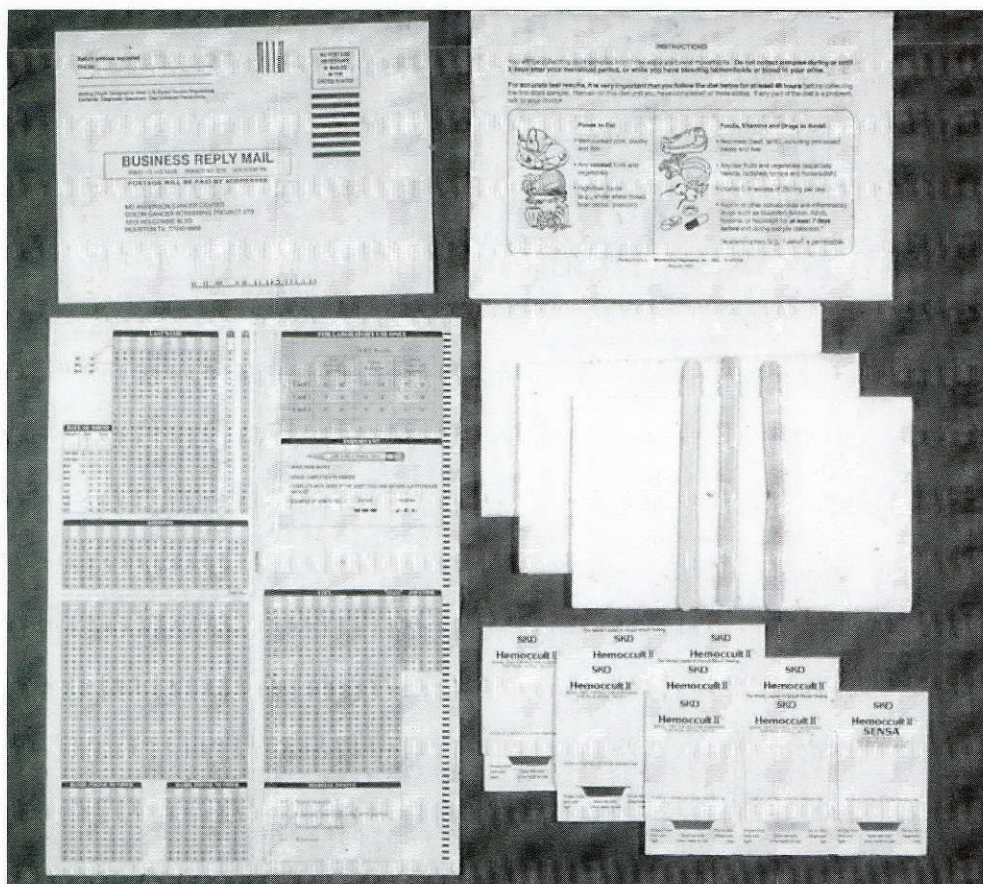
In the M. D. Anderson study, kits for each of the three tests were given to over 85,000 people by a Houston pharmacy chain and various minority community groups. Radio and television public service announcements and videos at the test distribution sites explained the FOBT procedure

and its importance. Every day for three days, each subject placed a pea-sized stool sample on a special card for each of the tests. (Collecting samples for three days increases the probability of detecting intermittent bleeding.) “It was complicated, but not as hard as using a VCR,” joked Levin.

The study showed that the rehydrated Hemoccult® test had the highest positivity rate but the lowest positive predictive value. (The positivity rate is the percentage of all test results that are positive, whereas the positive predictive value is the percentage of positive test results in patients shown by colonoscopy to have colorectal cancer.) The nonhydrated Hemoccult® test had the lowest positivity rate and the highest positive predictive value. The Hemoccult® Sensa® had a positive predictive value nearly as high as that of the nonhydrated Hemoccult®.

However, only about 13% of the study’s subjects completed the tests. One reason for the low response, said Levin, is that using nine test slides may have made the test too complicated. “People are also scared about getting a positive test, so they don’t want to be involved in any kind of colorectal cancer screening,” he said. To address this problem, Levin and his colleagues at M. D. Anderson and around the country are about to begin a national program through the Digestive Health Initiative to inform the public of the importance of testing for colorectal cancer. Their efforts would be easier if there were a celebrity spokesperson for colorectal cancer awareness, as there is for breast cancer and prostate cancer. Immediately after President Reagan had his colon polyps removed, colorectal cancer screening increased temporarily.

Even when people are more aware of the importance of colorectal cancer testing, they may still be reluctant to do the FOBT because they must collect stool samples. Using one type of



The testing kit used in M. D. Anderson’s comparative study of three types of FOBTs.

“It’s the adequacy of follow-up and the management of the condition afterward that are most important.”

over-the-counter test is appealing because there is no direct contact with stool. (The test is performed by dipping a test strip in the toilet basin containing the stool.) While Levin is in favor of making colorectal cancer tests as widely available as possible, he doesn’t recommend the over-the-counter FOBT because it is less accurate than the physician-administered tests and not well standardized and because there may be no one to help the patients interpret and follow up on the home tests. “I’m a great believer in people having the right to control their own destinies,” he said. “But I advise that they get tested for colorectal cancer through a physician or nurse, someone trained to judge their overall risk for developing the cancer. It’s the adequacy of follow-up and the management of the condition afterward that are most important.”

Positive FOBT warrants further testing

Surprisingly, many patients who get FOBTs through physicians aren’t getting the proper follow-up. A disturbing finding of the M. D. Anderson study was that only 59% of the patients who had positive FOBTs received either colonoscopy or the combination of flexible sigmoidoscopy and a double-contrast barium enema, the follow-up procedures recommended by the American Cancer Society. Significantly more gastroenterologists than other doctors provided the recommended follow-up. As might be expected, more cancers were detected among those who received the recommended follow-up than among the other patients. (See the box on page 4 for recommendations on how primary care physicians can use and follow up FOBTs.)

Advances in colon visualization have made follow-up of positive FOBTs less disagreeable to patients. In sigmoidoscopy, which can be performed by trained family physicians, a flexible scope has replaced the rigid scope, which many patients found uncomfortable. Sigmoidoscopy costs about \$150. Unlike sigmoidoscopy, colonoscopy is performed under conscious sedation by a gastroenterologist. It can take as little as 15–20 minutes if performed by an experienced

gastroenterologist. Colonoscopy costs about \$1000 and, as a follow-up to a positive FOBT, is covered by some insurers. One advantage of colonoscopy is that any polyps observed during the procedure can be removed immediately.

Ronelle A. DuBrow, M.D., of the M. D. Anderson Department of Diagnostic Radiology, is implementing a virtual colonoscopy system that will be even less invasive than regular colonoscopy and may not require pretreatment with laxatives, as the current visualization systems do. Virtual colonoscopy uses computerized tomography and computer technology to make a two- or three-dimensional image of the colon.

Genetic testing may complement the FOBT

Virtual colonoscopy is only one example of how researchers and physicians at M. D. Anderson are trying to improve colorectal cancer testing. “M. D. Anderson is conducting research on new technologies and evaluating ways to use existing technologies in the community,” said Levin. “We have a dual role and a dual responsibility.”

Genetic testing for colorectal cancer is on the horizon. About 6–10% of patients with colorectal cancer have inherited an increased tendency to develop it. Such patients can be identified by their family histories, as they usually have one or more first-degree relatives (mother, father, sisters, brothers, or children) who have had colorectal cancer. If the genetic change that caused colorectal cancer in their relatives can be identified, the rest of the family can be tested for the change to determine whether they too have inherited it and thus an increased propensity to develop colorectal cancer.

As with all genetic testing, the crux is determining what genetic change causes the disease. However, counseling is also an integral part of testing programs. Good genetic counseling must include risk analysis for the patient and family, education, and follow-up counseling on test results with all involved family members.

Many M. D. Anderson researchers are studying the genetics of colorectal cancer; they include

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Christopher I. Amos, Ph.D., and Xifeng Wu, M.D., Ph.D., of the Department of Epidemiology; Marsha L. Frazier, Ph.D., Patrick M. Lynch, J.D., M.D., and Gideon Steinbach, M.D., Ph.D., of the Department of Gastrointestinal Oncology and Digestive Diseases; Ellen R. Gritz, Ph.D., and Susan K. Peterson, M.P.H., of the Department of Behavioral Sciences; Sen Pathak, Ph.D., of the Department of Cell Biology; John M. Skibber, M.D., of the Department of Surgical Oncology; and Li Kuo Su, Ph.D., of the Department of Tumor Biology. There is also a collaborative M. D. Anderson–Johns Hopkins project in which researchers are screening stool specimens for malignant cells containing gene mutations.

In the meantime, FOBTs and flexible sigmoidoscopy have a central role in preventing death from colorectal cancer. “Screening for colorectal

cancer reduces mortality,” said Levin. “As inconvenient and, at the moment, as imprecise as the FOBT is, it nevertheless saves lives. We want to encourage the public and primary care physicians to use FOBTs and flexible sigmoidoscopy. I began my career as a gastroenterologist, and I treated a lot of patients with late-stage disease. Now I’d like to help prevent some of that disease.”

—MAUREEN E. GOODE

REFERRALS. Physicians who desire additional information may write Dr. Levin or Ms. Johnson, Division of Cancer Prevention, Box 203, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 792-0990. To refer a patient to M. D. Anderson, call the New Patient Referral Office at (800) 392-1611 or (713) 792-6161.■

How primary care physicians can test for colorectal cancer

Primary care physicians have a vital role in identifying colorectal cancer at its earlier, treatable stages. Here are some recommendations for colorectal cancer screening:

1. **Ask your patients if they have relatives with colorectal cancer.** Because of their increased risk of developing colorectal cancer, individuals with one or more first-degree relatives who have colorectal cancer should be under the care of a gastroenterologist and be monitored by colonoscopy, not FOBTs, at periodic intervals determined by their gastroenterologists.
2. **Prescribe colonoscopy, not FOBTs, for symptomatic patients.** The symptoms of colorectal cancer include rectal bleeding, change in bowel habits, abdominal pain, nausea, vomiting, weakness due to anemia, rectal pain or pressure, and narrowing of stool.
3. **Make the FOBT part of your annual examination of asymptomatic patients age 50 or older without a family history of colorectal cancer.** Use nonhydrated guaiac-based kits that test stool samples. “Nurses can have a very important role in reminding physicians and patients about annual exams,” said Constance Johnson.
4. **Recommend flexible sigmoidoscopy every 5 years for asymptomatic patients age 50 or older.** Levin commented that primary care physicians should be proficient in performing this examination. He expressed the hope that Medicare would reimburse physicians for this procedure in the future.
5. **Encourage all patients who have positive FOBTs to have colonoscopy or flexible sigmoidoscopy and barium enemas.** Refer them to an experienced gastroenterologist.
6. **Remind patients with polyps, adenomas, or colorectal cancer to have periodic colonoscopy** at the intervals recommended by their gastroenterologists.

—MAUREEN E. GOODE

Cancer genetics program

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sider the merits of potential prophylactic interventions. When prevention is not possible, however, the next goal is to initiate early detection and curative interventions.”

The Human Clinical Cancer Genetics Program also is looking at genes involved in susceptibility to colon cancer. As new predisposing genes are identified, the program will be extended to include other cancers as well. Individuals can be referred to the program by a physician, or they can contact the institution themselves.

Program to screen for *BRCA1* and *BRCA2* mutations

The program will initially focus on mutations of the breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2*) genes. The involvement of *BRCA1* in the development of breast and ovarian cancer was first recognized about five years ago. Four years later, the gene was successfully cloned, providing researchers with a better understanding of its activity. About 60% of individuals who have a mutation of *BRCA1* will get ovarian cancer in their lifetime; about 80% will get breast cancer. In addition, the risks for colon and prostate cancer are three to four times higher in individuals who carry the *BRCA1* mutation than in the normal population. So a person who carries a mutation in this gene should be counseled about screening options for all these types of cancer.

Mutation of *BRCA2* causes a higher incidence of breast cancer than ovarian cancer as well, particularly among young adults. And although breast cancer is rare in males, it does occur in some men with an abnormal *BRCA2* gene. “Any individual—man or woman—with a family history of male breast cancer should be counseled for the possible presence of a *BRCA2* mutation,” Mills said.

Counseling complements genetic testing

The breast/ovarian cancer pilot project involves three visits to M. D. Anderson: for risk assessment, pre-test counseling and genetic testing, and post-test counseling. It takes about six weeks to complete the program.

Risk assessment. During the risk assessment visit, Mills or Strong, along with Paula Rieger, M.S.N., certified nurse practitioner, interviews

the individual to determine such factors as: 1) overall family structure and occurrences of cancer in relatives, 2) how close in relation the individual is to any cancer patients, 3) the ages of the patients at diagnosis, 4) the types of cancer diagnosed, and 5) the number of cases of different types of cancer. With this information, a pedigree, or family medical chart, is developed and used to assess the individual’s potential risk of carrying the mutation that causes breast or ovarian cancer. “Low risk” means there is a 1% chance or less that the individual carries the mutation, and “high risk” means there is a 10% or greater chance. “Moderate risk” means either that the individual’s risk falls somewhere between low and high or that there is insufficient information to assess risk. For example, a 34-year-old woman can be assumed to be at high risk for breast cancer if her mother, two of her mother’s three sisters, and her grandmother were all diagnosed with the disease. However, if this same woman could recall only one family member in two generations who had cancer, a 58-year-old distant cousin with colon cancer, she would be determined to be at low risk.

An inherited abnormality in one or more genes does not guarantee a diagnosis of cancer. “There is not 100% penetrance; there are other factors that determine whether or not cancer occurs,” Mills said. “However, someone who inherits an abnormality will essentially be at increased risk for his or her whole life.”

Individuals considered to be at high risk receive genetic counseling, which includes education about cancer and genetic testing, discussion of risks and benefits of testing and implications of test results, exploration of surveillance and surgical options, and assessment of need for psychological or psychiatric intervention. Individuals determined to be at high or moderate risk would be offered enrollment in a surveillance program through the clinic, such as yearly mammograms.

Genetic testing. It is not uncommon for individuals to forgo genetic testing, Mills said. “This area of research is still new, and it generates mixed opinions.” The concerns and emotions that a participant may face are described in the informed consent form for the program (see the box on page 6). “Most of the time, all we can deliver is bad news or no news, and many people may simply not want to know that they may be at high risk of cancer,” Mills said. “Many may consider cancer a matter of chance that cannot be altered anyway; others may be burdened by the

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Informed consent explains concerns about genetic testing

Genetic screening is a complex issue, and helping people make informed decisions about participating in this type of study can be challenging. Drs. Mills and Strong and their colleagues have carefully described the procedure, its benefits, and associated risks in the informed consent document that each participant will read and sign. The section of the form that describes risks is reproduced here. In constructing the form, and particularly this section, the study team has tried to be sensitive to the varying cultural, educational, and social factors that are likely to influence potential participants' decisions.

Risks, Side Effects, and Discomforts to Participants: Many people are pleased with genetic testing, whether the results are positive or negative, because it allows them to plan their lives with regard to their cancer risk. However, for others, finding out that they have a change in a gene that is linked to higher risk of cancer may make them feel angry or shocked. They may deny that they have the abnormal gene. They may worry about their own health and that of family members. They may worry about passing the gene on to their children. They may feel that getting and keeping a job will be much harder. They may have different feelings about themselves. They may worry about medical costs and insurance.

Finding out that gene changes linked to higher risk of cancer are not present may cause a person to feel guilt or joy.

If the person does have the changed gene, he or she may decide to tell other family members who may also have the changed gene. This may not be welcome news to others in the family.

During counseling, other news about family issues may be revealed as a result of the testing and of the person finding out the test results. These issues may have to do with adoption or paternity (father's identity). Knowing such things may cause changes in a person's relationships with other family members. Information of this type will not be revealed to people in the study unless it will affect medical or childbearing decisions.

If people know they have the changed gene, they may have to make this known to an insurance company when applying for a policy. An insurance company may refuse to cover a person or may charge a higher price for insurance. Legislation to correct this potential problem is pending.

If an employer learns of the test results, a person may be denied a job offer.

Although the changed gene increases the chance that cancer will develop, not all people with the changed gene will get cancer. It is not known when cancer may occur in people who have the changed gene.

Not all the changes in a gene that may increase the risk for cancer are known. A change in a gene may be missed. There may be other genes linked to breast cancer and ovarian cancer that haven't been found or studied yet.

Results of gene testing may be unclear. The person may complete the test without learning more about his or her own risk of getting cancer.

Errors may occur in the laboratory.

If no changes in the gene are found, the person still has the same risk of getting breast cancer or ovarian cancer that all people in general have.

Cancer genetics program

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guilt that they may test negative but another relative may test positive.” Until appropriate laws are passed, another major concern patients may have is insurance discrimination. Furthermore, the efficacy of current screening or prevention procedures is as yet unclear.

Other participants are excited about the possibilities that testing offers and anxious to take advantage of whatever prevention or screening mechanisms are available, even investigational ones. Some people agree to testing but opt not to know the results; however, their participation still benefits the research effort.

For the genetic test, a blood sample is drawn from the individual and tested for the presence of a mutated *BRCA1* or *BRCA2* gene. “The best tests have a 30% false-negative factor, which means that about 30% of individuals who show no mutation in the test could still have an altered *BRCA1* or *BRCA2* gene and be at a high risk to develop cancer,” Mills said. “However, this test can detect 70% of the abnormalities in *BRCA1* or *BRCA2* that contribute to breast and ovarian cancer. We think it is remarkable that within the short period of time testing has been available, we can accurately detect such a large percentage of these genetic mutations.”

Post-test counseling. The final step in the program is post-test counseling and assessment. During this visit, the physicians discuss the test results and make recommendations for follow-up. Some patients will be referred back to their regular physicians, Mills explained, whereas others may be referred to M. D. Anderson’s breast or gynecologic clinic for further screening. “The news may be ‘Yes, you have the altered gene, and we recommend further screening and assessment.’ Or it may be ‘No, you don’t have the altered gene.’ At other times, when the results are not conclusive enough to determine risk or there is potential for a false negative, we end up saying, ‘You may not have the altered gene, but we must still consider you to be at potentially increased risk.’ Our advice would then be that they enter a surveillance program and follow prevention guidelines for the general population.”

In both pre- and post-test counseling, the potential impact on the psychological well-being of the participant and his or her family members is discussed. “Learning one’s genetic risk of get-

ting cancer may be as emotionally and physically stressful as accepting disease diagnosis,” said Mills. “We explain what the participants can expect as far as lifestyle changes and advise them on coping with those changes.” Psychological or psychiatric consultation is available for individuals who experience distress as a result of the genetic testing.

Mills explained that the Human Clinical Cancer Genetics Program adheres to the guidelines of M. D. Anderson’s institutional review board. “We are aware of and sensitive to the negative ramifications a positive screening for breast or ovarian cancer could have on an individual’s insurability, employability, and personal life,” he said. “Any information generated through our program will be maintained exclusively for the private use of the participant and his or her physician.”

Program will support cancer research efforts

Understanding the heritable genetic changes that can lead to the onset of cancer is an important step in the development of new, more effective cancer prevention, diagnostic, and treatment strategies, Mills said. “Data from some preliminary studies indicate that cancers resulting from an inherited abnormality may behave differently from cancers resulting from sporadic mutations. The information we obtain through the breast/ovarian cancer pilot project will help us determine, for example, whether these different types of cancers require different treatments.”

As important as the research effort, however, are the implications for patient awareness, said Mills. “People get really excited about genetic testing because it is new and because, as a screening mechanism, it has the potential for revolutionizing our approach to cancer. But as important are the steps that lead to and follow testing—risk counseling, genetics counseling, and treatment counseling. Key outcomes of this program will be communicating the information individuals need to make appropriate decisions and providing the support they need to cope with the prospect of cancer.”

—VICKIE J. WILLIAMS

REFERRALS. Physicians who have questions may call Christie Cook, administrative manager, at (713) 745-8045 or Paula Rieger, certified nurse practitioner, at (713) 745-8044 or write to them at Box 51, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030. To refer a patient, call the New Patient Referral Office at (800) 392-1611 or (713) 792-6161. ■

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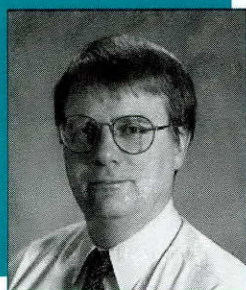
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Genetic counseling and testing help patients evaluate cancer risk

New program focuses on inherited predisposition to breast and ovarian cancer

Cancer Genetics



Gordon Mills is chairman of the Department of Molecular Oncology

One of the most important outcomes of cancer research in recent years has been a clearer understanding of the role of genetics in the development of cancer. Studies have shown that about 5–10% of all cancers can be attributed to genetic changes that are inherited in some families. Within the past five years, scientists have identified and cloned some of the genetic mutations that have been shown to run in families. As part of its ongoing cancer prevention program, M. D. Anderson Cancer Center has established a Human Clinical Cancer Genetics Program to study heritable genetic mutations that predispose certain individuals to cancer. The initial focus will be on the mutations that cause breast and ovarian cancer.

Goals are prevention and early detection

The breast/ovarian cancer pilot project of the Human Clinical Cancer Genetics Program is designed to help individuals whose family history suggests a predisposition to cancer evaluate the risk of disease development and determine whether surveillance or interventions are appropriate. Gordon Mills, M.D., chairman of the Department of Molecular Oncology, and Louise Strong, M.D., geneticist and professor of experimental pediatrics, are codirectors of the new program, which was established under the Division of Cancer Prevention. “The basis of our program is cancer prevention,” Mills explained. “Our goal is to help individuals assess their risk for breast and ovarian cancer so that they will be able to con-

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