

Missouri Cancer Care Perspectives

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MCC Initiates Genetic Screening & Counseling Program

Pre-printed forms available to referring physicians help identify those at risk for specific cancers

DNA may be the staff of life, but genomics — the study of all genes and their functions — lies at the root of cancer. It is for that reason that Missouri Cancer Care initiated its Cancer Risk and Genetics Program earlier this year.

Myriad Genetics Laboratories Inc., a national leader in genetics testing, is collaborating with MCC on this project.

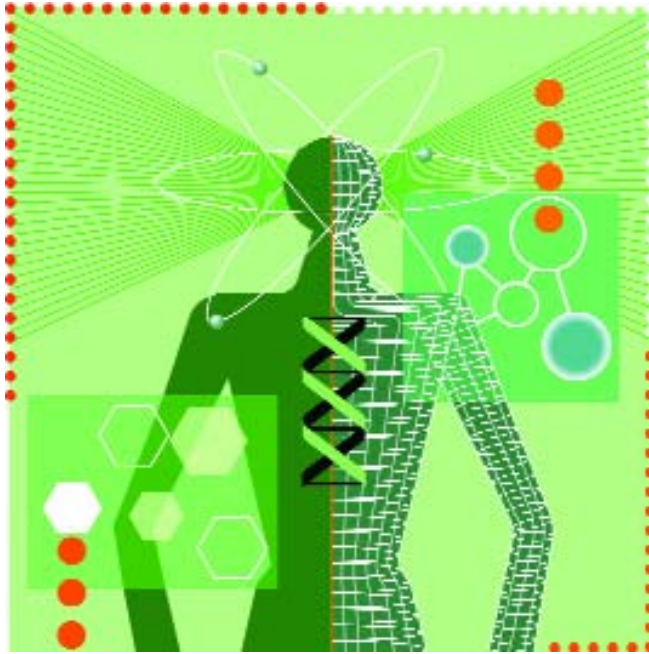
Some insurance carriers cover the cost for genetic testing. Pre-determination is recommended, however. Currently, there are 20 patients enrolled in the local program.

"It's been an interest of ours to develop a program to identify and counsel specific patients at risk for malignancy regarding the availability and appropriateness of genetic testing," said Tim Pluard, M.D., medical oncologist and program director. "Then we can advise patients what measures they can take preventively, to either reduce their risk of hereditary disease or to facilitate its early detection."

Increased surveillance often involved

For women at high risk of developing breast cancer associated with BRCA-1 or BRCA-2 genetic mutations, increased surveillance measures could include yearly MRI of the breasts rather than mammography. For persons at risk for colon cancer, specifically hereditary non-polyposis colorectal cancer, detection measures include earlier and more frequent colonoscopies.

Currently the Cancer Risk and Genetics Program is limited to breast and colon cancer syndromes. Most patients are referred by primary care physicians, gynecologists or gastroenterologists. MCC has developed pre-printed forms to



help referring physicians screen by family history and identify those persons who might be appropriate candidates for the program.

"The program involves pre-test counseling, identification of high-risk individuals, laboratory testing followed by post-test counseling relative to (test) results — whether they prove positive, negative or indeterminate," added John Wilkes, M.D., medical oncologist.

"We can provide the genetic test, facilitate testing and the interpretation of results to help reduce the incidence of cancer in people we identify as being at high risk (for inherited disease)," continued Dr. Pluard. "That's probably 5 to ten percent of all breast cancers, and 5 percent of all colorectal malignancies. It may not sound like a lot, but (extrapolated) nationally, if there are 200,000 newly diagnosed breast cancers each year, 20,000 of those cases could be prevented," he said.

"There is data (now) available that shows prophylactic removal of the ovaries reduces the risk of ovarian cancers as well as breast cancer by 90 and 50 percent, respectively. Similarly, prophylactic mastectomy reduces the risk of breast cancer by over 90 percent, in high-risk women."

Physicians interested in more information about the Cancer Risk and Genetics Program or wanting to obtain its pre-printed forms, should contact MCC. ■

Hereditary breast and colorectal malignancies are initial focus

Two New Treatments Highlight National Meeting Of Oncologists

Avastin & Erbitux share spotlight at ASCO; MCC participated in studies

Two new types of cancer treatment shared center stage at the 39th annual meeting of the American Society of Clinical Oncology (ASCO). Both prolonged survival of persons with colon cancer in clinical trials. Both were monoclonal antibodies: Avastin, produced by Genentech, and Erbitux of Imclone Systems.

Missouri Cancer Care participated in both the Avastin trial, and in a recently completed study of Erbitux for patients who failed all prior chemotherapy. Despite promising results, neither agent is commercially available yet. In fact, MCC is the only site between Indianapolis and Kansas City where patients can receive Erbitux through a compassionate-use study. At present, eligible patients are selected through a national lottery due to a limited supply of the experimental monoclonal antibody.

Monoclonal antibodies (MABs) are genetically-produced antibodies that attach to specific antigens. Antigens are substances — proteins, in this instance — secreted by the tumor that sit on the surface of cancer cells.

MABs are designed to disable or destroy designated proteins that control the growth of the cancerous cell. They can be used alone or with chemotherapy. Because they are "targeted" approaches, MABs typically produce fewer side effects than chemotherapy. Success is elusive, however, as cancer cells often contain several different growth pathways.

Avastin starves tumor, improves patient survival

Avastin prevents the production of new blood vessels that feed tumors in colon cancer by targeting a protein known as vascular endothelial growth factor (VEGF). VEGF is produced by cancer cells and causes new blood vessels to grow into the tumor. "By blocking this protein, the tumors are 'starved' of new blood supply and can no longer grow," explained Tim Pluard, M.D., medical oncologist and principal investigator at MCC. Clinically this process is known as anti-angiogenesis.

"Inhibition of angiogenesis as a means of treating cancer was first suggested 30 years ago by Harvard University scientist, Dr. Judah Folkman," continued Dr. Pluard. "Avastin is the first successful treatment based on this theory."

Avastin results are based upon a randomized, double blind study of 815 patients with stage IV colon cancer. Patients were either given Avastin plus standard chemotherapy — specifically a combination of irinotecan, fluorouracil and leucovorin (IFL), or IFL and a placebo.

When combined with IFL, Avastin increased median survival to 20.3 months from 15.6 months. Put another way, Avastin increased longevity for those with late-stage disease by 30 percent. "While certainly not a magic bullet, this is a remarkable improvement," said Dr. Pluard. "Some (of our) patients who continue to respond, remain on treatment."



Tim Pluard, M.D.

From Our Point Of View

Gene-based therapies gain momentum

Researchers have speculated that gene-based therapies may hold the key to more effective treatments for cancer. Data from clinical trials is beginning confirm that theory as new "targeted" approaches are validated. Progress is slow, however. At present, there are only five targeted therapies approved by the FDA.

This issue of Perspectives details a new, familial genetics risk-assessment program at Missouri Cancer Care. It also highlights the recent ASCO meeting, including study results of the first-ever angiogenesis inhibitor clinically effective in humans. The concept of angiogenesis inhibition, which deprives cancer cells of their blood supply, has been championed for over 30 years by Dr. Judah Folkman of Harvard. Dr. Tim Pluard, medical oncologist and principal investigator of clinical research at Missouri Cancer Care, worked as a research fellow in Dr. Folkman's laboratory. He also edited this newsletter and shared his unique "perspective" on genetically engineered approaches to cancer. At Missouri Cancer Care, we will continue to apprise you of promising experimental strategies and provide them, when possible. ■

Continued on back

MRI vs. Mammography

A pair of independent European studies reported that magnetic resonance imaging (MRI) was superior to mammography in detecting breast cancer in high-risk women. Findings were discussed during the plenary session of the American Society of Clinical Oncology (ASCO) conference, which highlights the most notable research findings of its annual meeting. However, an American researcher at Memorial-Sloan Kettering Cancer Center urged restraint before switching detection techniques in all women, due to the number of false positive findings associated with MRI. He presented a third trial's findings during a news conference at the meeting.

European studies show MRI more effective in detecting high-risk breast cancer

"Mammography is uniformly accepted in women over the age of 50," said Tim Pluard, M.D., medical oncologist. "Although there has been some dissension, most (parties) recommend mammography in women 40 to 50 years of age. It's in younger women where mammography is less effective because of the density of breast tissue.

"Screening with mammography in high-risk women has always been a concern because of its 'miss' rates," continued Dr. Pluard. "MRI is useful in finding lesions that are not detected mammographically." However, MRI is so sensitive it can detect tiny abnormalities that may not be cancers but benign growths. This prompts further testing and heightened anxiety. Therein lies the debate: Which imaging technique is superior?

MRI render higher cancer detection rate, but are less specific

To answer this question, German researchers at the University of Bonn conducted a five-year study of 45 women who carried, or were suspected carriers of the BRCA-1 or BRCA-2 genetic mutations based on strong family history. All women underwent a clinical breast exam, mammography, ultrasound and an MRI.

MRI examinations discovered 51 cancers but missed two malignancies over a five-year period rendering a 96 percent detection rate. Mammography had a detection rate of 43 percent and ultrasound, 43 percent. MRI was also associated with lowest rate of unnecessary biopsies. German researchers attribute this low, false positive rate to their extensive experience in breast MRI interpretation.

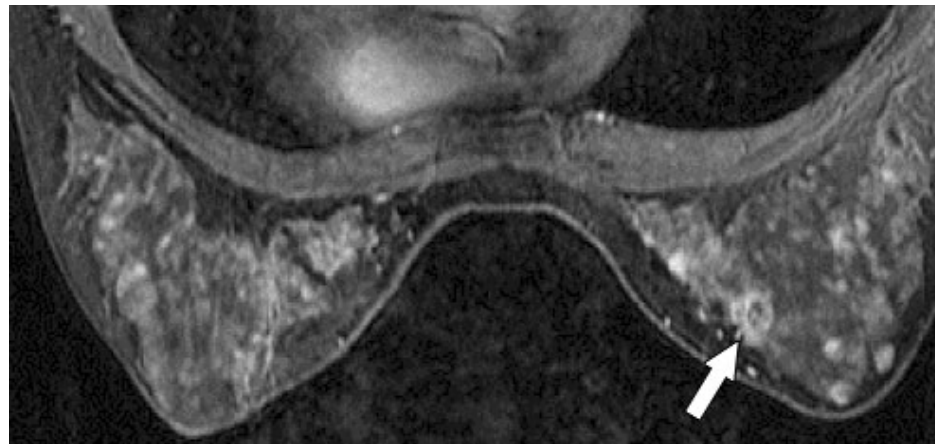
Dutch researchers reported similar findings in a study of 1,905 women at high risk of breast cancer due to either BRCA genetic mutation or a strong family history of disease. The study evaluated benefit of yearly MRI, mammography and clinical breast examination.

MRI was significantly more effective at

Genetic screening can help identify those who might better benefit from MRI

Factors Suggesting Hereditary Breast Cancer:

- Personal or family history of:
 - Early onset breast cancer (<35)
 - Bilateral breast cancer
 - Breast and ovarian cancer
 - Multiple pre-menopausal women with breast cancer
 - Male breast cancer



MRI scan with contrast demonstrating mass in right breast with surrounding enhancement.

Source: Delille JP, Slanetz PJ, Yeh ED, et al. Invasive ductal breast carcinoma response to neoadjuvant chemotherapy: noninvasive monitoring with functional MR imaging — pilot study. *Radiology* 2003; 228:63-69

detecting breast cancer. It found 71 percent of cancers. Mammography detected 23 percent of cancers; clinical breast exam found 16 percent. However, MRI was found to be less specific. It was more likely to produce false positive rates.

Dutch researchers recommend MRI in addition to mammography for young women with known BRCA genetic mutations because of the density of breast tissue, and their potential for developing rapidly-growing tumors.

MRI not for all women

MRI can detect very small tumors i.e. less than one centimeter in size. However, MRI can also detect many other abnormalities that may be benign but require a biopsy to make such a determination. A study from Memorial Sloan-Kettering Cancer Center in New York illustrates this point. Although it showed that MRI was 100% sensitive in detecting cancer, 20% of patients enrolled in the study needed a biopsy after their first MRI for lesions that, ultimately, were found to be benign.

Given this 20% false positive rate on first MRI scans, these researchers emphasized that that breast MRI should be used in conjunction with mammography and only in high-risk women either on the basis of mutations in BRCA1 or BRCA2 or very strong personal or family histories. Patients should also be advised of the false positive rate prior to the scan to minimize anxiety should a biopsy be necessary.

Genetic screening and counseling can help identify those who might best benefit from MRI.

"By identifying those women who carry the BRCA-1 or BRCA-2 mutations, we can further delineate a subset of women who might also best benefit from MRI," said Dr. Pluard. "Women with certain risk factors for either BRCA mutation should seek genetic screening and counseling." Missouri Cancer Care has such a program available. ■

Genetically-engineered protein prevents neutropenia

Shortening Treatment Intervals Improves Effectiveness Of Chemotherapy

Reducing the intervals between treatments can improve the effectiveness of chemotherapy in women with early-stage breast cancer. It can also reduce risk of recurrent disease, say researchers of a clinical trial conducted across the nation and sponsored by the National Cancer Institute.

Results of the trial were recently published in the *Journal of Clinical Oncology* (Vol. 21, No. 8, pgs 14331-1439).

The study compared the new approach known as "dose-dense" therapy against standard treatment for women having early-stage breast cancer with nodal involvement. Both groups used the same anticancer drugs — doxorubicin, paclitaxel and cyclophosphamide — but with different treatment schedules.

One group of patients received standard treatment i.e. chemotherapy every three weeks. The dose-dense group received chemotherapy every two weeks. The dose-dense group also received a genetically-produced protein (filgrastim) that stimulates the production of white blood cells depleted by chemotherapy. Neutropenia, a drop in the number of white blood cells, is a serious and common complication of chemotherapy sometimes resulting in hospitalization. Filgrastim helps prevent neutropenia and allows for dose-dense therapy.

Researchers found that women who received dose-dense therapy plus filgrastim were less likely to have a recurrence, experienced fewer cases of neutropenia and might live longer than those undergoing standard treatment.

"Previously you had to allow (21 days) for the bone marrow to recover from chemotherapy," said Tim Pluard, M.D., medical oncologist at Missouri Cancer Care. "But the premise is that you also allowed the tumor to regrow. Now you can shorten treatment intervals by using filgrastim which stimulates the bone marrow to produce more white blood cells."

An enhanced form of filgrastim called pegfilgrastim was approved earlier this year. It is administered the day after chemotherapy as a single subcutaneous injection. The most common side effect of pegfilgrastim during clinical trials was bone pain, which was managed by non-narcotic drugs. ■

'Dose-dense' therapy reduces risk of recurrence in early-stage breast cancer

Two New Treatments — from page 1

Trial results were particularly surprising given that an earlier study of Avastin in breast cancer patients did not yield benefit. Responses may be tumor specific. The most common side effect of Avastin was hypertension, which was easily managed with medication. Gastrointestinal perforation also occurred, though rare.

Eribitux validated in European study

Results from a European trial reported at the ASCO meeting confirmed that Eribitux does indeed work, validating an earlier Imclone-sponsored trial reaching the same conclusion.

The European trial involved 329 colon cancer patients who had failed to respond to irinotecan (standard chemotherapy). They were then given Eribitux and irinotecan, or Eribitux alone. The study found that 23 percent of those patients receiving combined therapy and 11 percent of those taking Eribitux alone responded to treatment. Responding patients' tumors shrank by at least half. Median survival was almost nine months for Eribitux plus irinotecan and seven months for Eribitux only.

Eribitux works by silencing chemical signals that allow a tumor to flourish. It accomplishes this by blocking the communication between a protein known as epidermal growth factor (EGF) and its receptor. This interaction is crucial to cell growth and survival in many of the most common solid tumors.

The most common side effect of Eribitux was an acne-like rash that resolves after treatment is stopped. ■

"MCC and our patients contributed to the two biggest stories coming out of ASCO this year."

Tim Pluard, M.D., medical oncologist & principal investigator

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