(Left to right) Medical oncologist Mark Robson, gynecologist Noah Kauff, medical oncologist Zsofia Stadler, and Clinical Genetics Service Chief Kenneth Offit are applying genetic insights to improve the care of cancer patients.

Summary

At Memorial Sloan Kettering, as the genetics revolution continues to flourish, discoveries made in the laboratory are increasingly producing real-world benefits for cancer patients.

As the genetics revolution continues to flourish, discoveries made in the laboratory are increasingly producing real-world benefits for cancer patients. At Memorial Sloan Kettering Cancer Center, genetic breakthroughs have changed how medicine is practiced, revealing new ways to dramatically reduce

cancer risk and improve the effectiveness of therapies.

“The scientific excitement here is very high,” said Kenneth Offit , Chief of Memorial Sloan Kettering’s Clinical Genetics Service. “Institutional leadership has made it clear that clinical genetics is a key aspect of our mission. It’s a work in progress — we’re implementing new insights in the clinic while we continue to make new research findings.”

Memorial Sloan Kettering’s Clinical Genetics Service now offers testing for more than 50 kinds of genetic variants linked to cancer. Information from these tests guides decisions on medical care for patients and families affected by cancers of the breast, ovary, colon, thyroid, eye, stomach, pancreas, and skin, as well as a variety of childhood tumors.

“Testing for inherited predisposition to cancer has become a broadly accepted part of clinical care,” Dr. Offit explained. “When we began genetic testing in the mid-1990s, the question often posed was ’What are you going to do with the information?’ It’s now become clear that we do a lot with genetics by tailoring cancer prevention and management.”

The Clinical Genetics Service began operating in the early 1990s, even before the identification of disease-linked genes such as *BRCA1* and *BRCA2*, which are associated with breast and ovarian cancer risk. (Dr. Offit and his research team discovered the most common mutation of *BRCA2* in 1996.) “ was the director of the service as well as its only member, seeing perhaps two dozen families a year,” Dr. Offit recalled. “Over time we’ve grown to a full-fledged clinical service with four physicians, eight genetic counselors, two fellows, and a research laboratory.” (The new service benefited greatly from the 1995 Annual Appeal of The Society of Memorial Sloan Kettering Cancer Center.)

In September 2007, Memorial Sloan Kettering made a landmark decision to obtain consent to include inherited genetic information in patient medical records. “A patient’s physician needs to see this information in order to provide the best care,” Dr. Offit said. He added that an important hurdle was cleared in May 2008 with passage of the Genetics Information Nondiscrimination Act, a federal law that makes it illegal for insurers and employers to discriminate based on genetic predisposition to disease.

Much genetic testing at the Memorial Sloan Kettering relates to germline (inherited) gene mutations, which are passed from parent to child. Because these mutations exist in every cell in the body, the risk of disease is greatly increased during the lifetime of people who inherit them. Memorial Sloan Kettering researchers also investigate somatic mutations — gene alterations that occur in the specific tissues that give rise to cancers. Testing mutations present in the tumor cells themselves can help diagnose cancer and also guide the development of treatments tailored specifically for those mutations causing disease. For both inherited and somatic genetic changes, mutations in genes can lead to cancer when the proteins encoded by the genes are altered in such a way that they contribute to the formation and/or survival of cancer cells.

At present, the Clinical Genetics Service focuses on testing for inherited mutations and providing support, in the form of genetic counseling, for patients before and after results are reported.

Clinical genetics is entering a new phase, as researchers discover gene variants that are far more common in the general population yet have low penetrance, meaning they confer a much more subtle effect on disease risk. “When we discovered the most common *BRCA2* mutation in 1996, it was found in 1 percent of the population studied but was associated with a risk of cancer 20 to 50 times higher than the risk in the general population,” Dr. Offit explained. “In contrast, genetic markers we are finding now are seen in 20 to 30 percent of the population but are associated with disease risk that is only slightly increased compared with the general population.”

The gene variants discovered today are being identified by scanning entire genomes — the full genetic material in an individual’s chromosomes. These variants also predict response to, and side effects of, therapies. Some genes may even be protective against cancer and other diseases. “Now that we have included genetic information in cancer care, a major challenge before us is how best to incorporate genomic risk assessment into practice,” Dr. Offit said.

Peridiagnostic Testing

Genetic testing at Memorial Sloan Kettering is increasingly being offered shortly after the time of diagnosis to inform treatment decisions at an early stage, a practice called peridiagnostic testing. The Clinical Genetics Service is now investigating women's choices in this situation. Medical oncologist Mark E. Robson heads a program offering prompt (within one week) *BRCA* results for a subset of patients — Ashkenazi Jewish women — with newly diagnosed breast cancer . (This population has three common mutations that can be checked rapidly.) The accelerated testing is performed at the Center in the Diagnostic Molecular Pathology Laboratory headed by molecular pathologist Marc Ladanyi .

Clinical Genetics Chief Kenneth Offit and genetic counselor Megan Harlan provide guidance to a patient.

The quick turnaround may in some cases guide surgical decisions. Many women diagnosed with breast cancer can have a lumpectomy in order to conserve the breast. If it were known that a woman carried a *BRCA* mutation, she might opt instead to have a bilateral mastectomy (removal of both breasts) as a preventive measure against a future breast cancer.

Giving patients genetic results at the time of diagnosis does raise concerns about their impact. Will patients who just learned they have cancer be able to evaluate genetic information carefully? Will they later second-guess the choices they made? To answer this question, Dr. Robson and Karen E. Hurley, a psychologist in the Clinical Genetics Service, have been studying the effect that peridiagnostic testing has on patients. "We want to see if individuals are satisfied with the decisions they made as a result of having genetic information — for example, the decision to have or not have a prophylactic mastectomy," Dr. Robson said.

Peridiagnostic testing for *BRCA* mutations has implications for ovarian cancer as well. Women testing positive for the mutations may be eligible to receive tailored treatments, and their family members who also test positive may wish to have their ovaries removed after childbearing is completed. Noah D. Kauff, a gynecologist and member of the Clinical Genetics Service, is leading an effort to offer *BRCA* testing to all patients at Memorial Sloan Kettering newly diagnosed with ovarian cancer. Peridiagnostic testing may also lead to the consideration of additional treatment options. For example, a class of drugs called PARP inhibitors appears to be especially effective in women with breast or ovarian cancer resulting from *BRCA* mutations. PARP is an enzyme that helps repair damaged DNA. The proteins encoded by *BRCA* genes also are involved in DNA repair, but on a different pathway. In *BRCA* mutation carriers, the cancer cells have lost most or all *BRCA* function, but the PARP pathway still functions. When treated with a PARP inhibitor, the *BRCA*-mutant cancer cells lose their remaining DNA-repair mechanism and appear to self-destruct. Early-stage clinical trials in both breast and ovarian cancer patients with a *BRCA* mutation have shown promising results with little toxicity.

"Decisions about preventive surgery and, in the future, decisions about other treatments are two very important, clinically relevant reasons why people with breast or ovarian cancer that may be due to *BRCA* mutations should get themselves genetically tested," Dr. Robson said. "The therapeutic implications now are very real."

Back to top

Family Matters

Memorial Sloan Kettering has increased efforts to involve family members in the diagnosis of hereditary cancers, for both clinical and research purposes. One approach has been to enroll families in registries for specific hereditary cancers. The registries allow for increased screening of high-risk patients and the collection of DNA and tissue samples and epidemiological data that could provide clues about what causes the cancer.

Medical Oncologist Manish Shah

In 2002, Memorial Sloan Kettering established a familial pancreatic cancer registry to help define inherited and environmental risk factors for the disease. (About 10 percent of pancreatic cancer cases are thought to be hereditary.) The registry enrolls patients in whom pancreatic cancer was diagnosed before age 50, as well as their first-degree

relatives. It also includes people thought to be at high risk for the disease based on its diagnosis in multiple first- or second-degree relatives, as well as people with *BRCA1* or *BRCA2* mutations who also have a family history of pancreatic cancer.

> These registries are very powerful tools to capture DNA and patient information so we can find new genetic risk factors.

Robert C. Kurtz, Chief of the Gastroenterology and Nutrition Service, said enrollees considered at high risk are screened yearly using MRI to look for lesions that can develop into tumors. If lesions are detected, physicians can follow up with more extensive testing and possibly a biopsy and — if cancer is found — remove part or all of the pancreas. “I look at these precursor lesions as being much like the colon polyps that lead to colon cancer ,” Dr. Kurtz said. “By finding these precursors, we have a window of time in which we can act before cancer develops.”

Pancreatic cancer is difficult to treat, and the disease is almost always fatal without intervention. “The overall five-year survival rate for pancreatic cancer in the United States today is about 4 percent — the same as it was 20 years ago,” he said. “With the registry, we hope to identify people with a precursor lesion, or at an earlier stage of pancreatic cancer.”

In 2005, medical oncologist Manish A. Shah set up a familial registry for gastric (stomach) cancer, enlisting people who were diagnosed with the disease before age 50 or who are considered at high risk based on family history. With guidance from genetic counselors Megan M. Harlan and Sarah Coombes, people included in the registry may also be tested for mutations in a tumor-suppressor gene called *CDH1*. *CDH1* has been linked to hereditary diffuse gastric cancer, a relatively rare subtype of hereditary gastric cancer. About 20 to 30 percent of those tested have the *CDH1* mutation.

Those who test positive for the mutation face a radical but potentially lifesaving decision. “Diffuse gastric cancer grows within the wall of the stomach, not on the surface, so it is very difficult to detect with endoscopy,” Dr. Shah said. “Because patients carrying the *CDH1* mutation have a high risk of developing the disease, we now recommend removal of the stomach in mutation carriers over the age of 30.”

Although this may seem like a drastic measure for a healthy person with no evidence of disease, surgical oncologist Daniel G. Coit has found that most patients who take this step maintain normal lives after making adjustments to eating habits. And the benefit is clear — examination of tissue taken from these patients usually reveals early signs of cancer.

The gastric and pancreatic cancer registries, and a similar registry of families with polyposis and colon cancer directed by colorectal surgeon José G. Guillem, are valuable in helping Memorial Sloan Kettering researchers gather genetic samples relating to hereditary gastrointestinal cancers. “These registries are very powerful tools to capture DNA and patient information so we can find new genetic risk factors,” Dr. Shah said. “Most gastrointestinal cancers have several potential causes, and the interplay between genetics and environment may lead to important insights regarding disease biology and development.”

Back to top ^

Casting a Wide Net

In particular, the DNA samples gathered by the cancer registries will play an essential role in the identification of new disease genes and gene variants. Robert J. Klein, a computational biologist recently recruited from The Rockefeller University, is collaborating with a number of Memorial Sloan Kettering clinicians, including Drs. Kurtz, Shah, and Offit, to pinpoint these genetic markers using a variety of approaches.

For example, Dr. Klein is examining DNA samples collected for the gastric cancer registry. Dr. Shah and colleagues hypothesize that a cause of some gastric cancers is infection with *Helicobacter pylori*, the bacterium linked to stomach ulcers, which can cause inflammation in the stomach. Dr. Shah and Dr. Klein are studying immune regulatory genes in people with intestinal gastric cancer to see if there are inherited factors that could alter the immune response to *H. pylori* — perhaps making the immune system overreact — and put this population at increased risk for the disease.

In other studies, Tomas Kirchhoff , a research associate in Dr. Offit’s laboratory, and other colleagues are using a powerful new tool called genome-wide association (GWA) mapping. The GWA approach looks for small differences in genetic markers spread throughout the entire genome, comparing the markers present in people with the disease against those who are unaffected. The markers are differences in a single genetic base pair called a single nucleotide polymorphism (SNP, pronounced “snip”). Analyses are usually performed on microarrays in the Genomics Core Laboratory of Agnès Viale in the Sloan Kettering Institute . A GWA analysis by Dr. Offit, Dr. Kirchhoff, and colleagues recently mapped a new breast cancer susceptibility gene on

chromosome 6.

The pancreatic cancer registry, with the help of epidemiologist Sara H. Olson, has collected enough DNA samples from people with the disease — as well as control samples from spouses, partners, and in-laws — to enable Memorial Sloan Kettering researchers to use the GWA approach in search of markers affecting risk of pancreatic cancer. “We haven’t had a strikingly positive result so far, but there are some interesting genes we’re going to follow up on,” Dr. Klein said. “We are going to add more samples and increase the power of the study.”

“Obviously, the Holy Grail would be to find a gene or genes that cause pancreatic cancer in these families,” Dr. Kurtz added. “It might not prevent the disease, but it could lead to better screening of at-risk individuals and give our scientists targets for treatment.”

Back to top

Somatic Mutations

Medical Oncologist Ross Levine

Memorial Sloan Kettering researchers also investigate somatic mutations, which are not inherited but are acquired in cells during a patient’s lifetime. Some of these mutations are associated with a large number of cancer types while others are specific to a certain disease. By comparing the genomes of tumor cells with the genomes of normal cells in the same patient, scientists can get clues about what has gone wrong in the tumor cells to cause them to multiply uncontrollably.

For example, Ross L. Levine , an oncologist and assistant member in the Human Oncology and Pathogenesis Program (HOPP), has studied the tumor cells of patients with blood cancers and compared them with noncancerous cells from the same patient. Genetic analysis showed that the tumor cells have a mutation in the gene for the signaling molecule JAK2. This finding allows his laboratory to focus on JAK2 activity and the pathway it regulates to improve therapies for patients with these disorders.

“These laboratory-based insights have incredible value,” Dr. Levine said. “We’re not going to come up with effective therapies until we understand which mutations are present in patients’ cells. I really believe genetic studies of human samples can be used to improve therapies for all kinds of cancers.”

In some cases, testing for somatic mutations has begun to play a role in treatment decisions. Several years ago, medical oncologist William Pao and Memorial Sloan Kettering President Harold Varmus led a team that found that certain somatic mutations in the gene *KRAS* predicted that patients with non-small cell lung cancer would not respond to treatment with gefitinib (Iressa®) and erlotinib (Tarceva®), small-molecule drugs that target mutated epidermal growth factor receptor (EGFR). The Molecular Diagnostics Service, led by Dr. Ladanyi, began clinical testing for *KRAS* mutations to determine which patients would benefit from these drugs and which would not, and this test is now standard at the Center. More recently, clinical *KRAS* testing has begun in colorectal cancers as well, because in this cancer KRAS mutations also predict which tumors will fail to respond to antibody treatments targeting the EGFR protein.

> These laboratory insights have incredible value. We're not going to come up with effective therapies until we understand which mutations are present in patients' cells.

Back to top

Future Uses of Genomic Testing

The Clinical Genetics Service recently received three large awards that will support genome-wide studies relating to cancer risk. The Starr Foundation is funding an international study led by Dr. Offit and epidemiologist Mia M. Gaudet that will analyze 5,000 DNA samples from women with *BRCA2* mutations, searching for additional genetic factors that may protect against breast cancer or make a person more susceptible.

Other studies in Dr. Offit’s laboratory will involve genomic analysis of families with lymphomas (cancers of the immune system), as well as those with cancers of the breast and colon who do not carry known mutations. Research in this area will be bolstered by the recently established Robert and Kate Niehaus Clinical Genetics Initiative . The initiative, created with a $5 million commitment from the Robert and Kate Niehaus Foundation, is helping to support recruitment of new researchers and research related to inherited cancer susceptibility.

Finally, the Breast Cancer Research Foundation is funding a project led by Dr. Offit and Memorial Sloan Kettering geneticist and medical oncologist Zsofia K. Stadler . This project will use a genome-wide approach to study mechanisms of susceptibility to colon, breast, and pediatric cancers and will also analyze how families make use of genomic cancer-risk information.

“The goal of all of these research efforts is to begin to use genomic risk markers to target cancer prevention, just as we have begun to target treatments based on genetic analysis,” Dr. Offit said.

Back to top