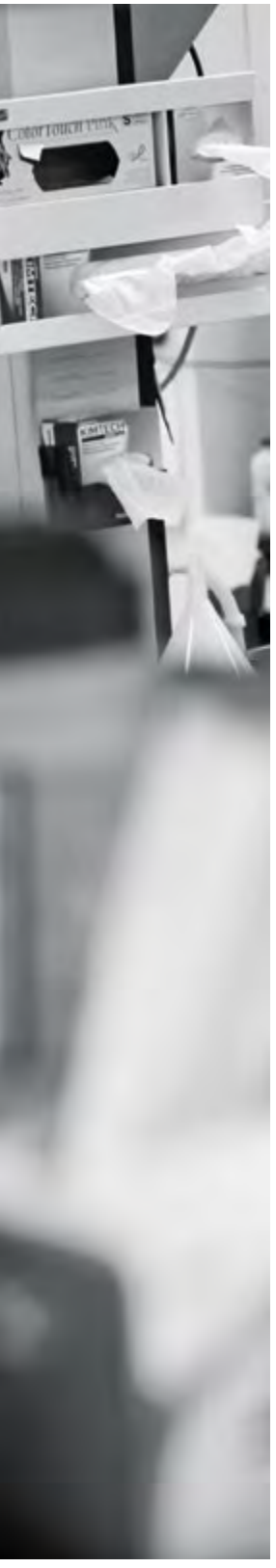
FOCUS ON

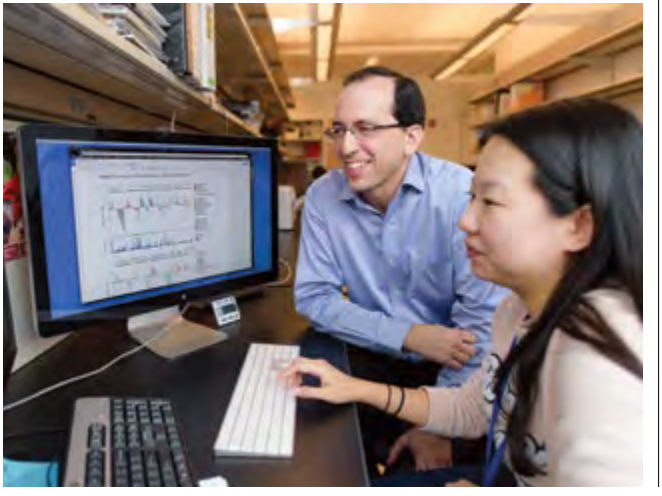
MSK-IMPACT

Knowing more about the changes that drive tumors helps open the door for precision oncology, in which a person is matched with a treatment that targets the specific weaknesses in the cancer. MSK's genetic-sequencing test, which provides those details, marked two major advances in 2017.

Genetic counselors like Meg Sheehan meet with patients and families to explain the inherited risks for cancer that are passed down through generations.

A SWEEPING IMPACT





GUIDING TREATMENT WITH DATA

Not all genetic mutations cause cancer. But some do, and thanks to rapid advances in technology, scientists have amassed a wealth of information about which genetic mistakes are most likely to lead to the disease. The most pressing challenge has been testing people for cancer-causing mutations — and handling the data produced as a result.

MSK-IMPACT™, a genetic-sequencing test, is MSK's answer to this issue. Doctors can use it to probe a tumor for mutations and other genetic changes in 468 genes that are seen in both common and rare cancers.

Currently, all MSK patients with advanced solid tumors have their cancer tested by MSK-IMPACT, which has been in use as a clinical test approved by the New York State Department of Health since 2014. The test hit two major milestones in 2017: authorization from the US Food and Drug Administration as a tumor-profiling test, the first test of its kind to receive this designation; and the publication of data from the first 10,000 people whose tumors were sequenced.

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>
> –MICHAEL BERGER

Far left: Marc Ladanyi (*right*), with molecular geneticist Liying Zhang (*left*) and pathologist Diana Mandelker, played a key role in the authorization of MSK-IMPACT. *Left, top*: The Biomek FXp machine uses unique bar-code sequences to tag patients' DNA, which will be sequenced using molecular testing like MSK-IMPACT. *Left, bottom*: Michael Berger, with computational biologist Helen Won, helped lead the development of MSK-IMPACT.

"These landmark achievements are the result of a major collaborative effort," says geneticist Michael Berger, who led the development of the test and is an Associate Director of the Marie-Josée and Henry R. Kravis Center for Molecular Oncology (CMO). "In addition to guiding treatment choices, this test is producing valuable insights about how cancer grows and resists treatment."

"MSK-IMPACT has allowed us to establish an entirely new paradigm for cancer care," says Marc Ladanyi, Chief of the Molecular Diagnostics Service. Dr. Ladanyi's team, including molecular pathologist Maria Arcila, was responsible for the clinical validation of the test and now oversees its performance as well as the analysis and interpretation of the test results. "In this new paradigm, it is critical not only to identify the exact type of cancer someone has and how far it has spread but also to determine the mutations that drive cancer cells to divide," Dr. Ladanyi adds.

MSK-IMPACT makes it possible for precision oncology to take place. Also called personalized medicine, this approach is based on the idea that the genetic alterations that drive cancer cells to grow can be targeted with specific drugs. The test has also allowed investigators to undertake basket studies. While traditional clinical trials focus on a particular cancer type, basket studies concentrate on a specific mutation found in the tumor, regardless of where the cancer originated in the body.

This type of testing is already changing how people are treated. In May 2017, MSK investigators published the aforementioned study in *Nature Medicine*, showing that nearly 37 percent of the first 10,000 people who had their tumors sequenced using the MSK-IMPACT test had at least one actionable mutation, which means drugs were available that precisely targeted the mutation. According to the study, about 11 percent of the people with actionable mutations participated in clinical trials involving molecularly targeted therapies as a direct result of MSK-IMPACT. Still others received immunotherapy based on their results.

"The breadth and depth of MSK-IMPACT has allowed us to detect important genomic alterations that would have been missed by other approaches," says David Solit, Director of the CMO, which financially supports the bulk of MSK-IMPACT testing.

LOOKING FOR CANCER DRIVERS

Although MSK-IMPACT was developed largely to aid in diagnosis and to guide treatment, investigators knew from the beginning that the information they were collecting could be instrumental for research. Everyone who has had a tumor sequenced by MSK-IMPACT — more than 24,000 people to date — has had their genetic data linked to clinical records showing how they fared after treatment.

"This is a huge data set," Dr. Berger says. "It's extremely valuable to labs that are studying specific genes and biological pathways that are important in cancer. They can focus their research on the most frequently observed mutations, rather than having to guess which mutations may be the most important."

Beyond using those priceless data in MSK's own labs, it's equally important to share them with other organizations to move cancer research forward as quickly as possible. One of these efforts is AACR Project GENIE, initiated by the American Association for Cancer Research and spearheaded by Charles Sawyers, Chair of MSK's Human Oncology and Pathogenesis Program. This multicenter effort strips patient-identifying information from the records, then pools the information for analysis, allowing researchers across the nation to study the data. The resource enables them to discover new links between cancer-related genetic mutations and patient outcomes.

In January 2017, Project GENIE announced the release of its first batch of data: genomic-sequencing information on tumors from nearly 19,000 people with cancer, linked to information about their clinical care. These data, now up to 38,000 people, will help researchers figure out which mutations are drivers (changes that actually induce cells to grow out of control) and which are passengers. Knowing the difference is crucial to developing effective cancer drugs.

"Many of the mutations linked to cancer are rare, making it difficult for one institution to collect enough data to make statistically significant connections between a particular mutation and its role in causing cancer," Dr. Sawyers says. "There is a great value in joining together and pooling the insights that we're gaining from sequencing patient tumors."

Above: Maria Arcila, Director of the Diagnostic Molecular Pathology Laboratory, helps oversee the use of MSK-IMPACT. *Right*: Charles Sawyers, with research fellow Elizabeth Adams, is part of an international collaboration among research institutions that shares data from genetic sequencing.

> It was a tremendous effort to develop MSK-IMPACT, orchestrated by many people with diverse backgrounds.”
>
> –AHMET ZEHIR

Ahmet Zehir has participated in a number of studies relating to MSK-IMPACT and how it’s being used.

FAR-REACHING VALIDATION

Before MSK-IMPACT, next-generation sequencing technology had been used mainly in the context of research studies. The pathologists, technologists, and bioinformaticians on the development team worked painstakingly to create and enhance methods for collecting and analyzing clinical samples, which present a much greater challenge. Moving such a complex research test into the diagnostic laboratory setting was a major advance.

“It was a tremendous effort to develop MSK-IMPACT, orchestrated by many people with diverse backgrounds,” says Ahmet Zehir, Director of Clinical Bioinformatics.

The FDA recognized this innovation when it authorized MSK-IMPACT as a tumor-profiling test in November 2017. A benefit of this designation, which is given to some medical devices and laboratory-developed tests, is to set up the test as a model and establish standards for the development and validation of similar tests in the future.

This validation could lead to broader insurance coverage for genomic-sequencing panels in cancer — a huge issue if these tests are to be widely accessible.

“People making reimbursement decisions for Medicare and private insurance companies are realizing that this kind of sequencing is a bargain because patients can receive all the information they need to get the right treatment from a single test,” says David Klimstra, Chair of the Department of Pathology. “We’re optimistic that as the positive impact of genetic sequencing becomes more apparent, we’ll be able to use the test to benefit more people.”

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BRANCHING OUT TO THE FAMILY TREE

While the MSK-IMPACT test was established primarily to screen for mutations in tumor cells, it also offers the opportunity to better understand the contribution of inherited cancer-related genes among people with cancer and their families. For Mitchell Katz, 64, findings from MSK-IMPACT helped researchers understand why he responded so well to a new immunotherapy drug and, more importantly, may have saved the lives of several of his close family members.

Mr. Katz was first diagnosed with urothelial cancer in one of his kidneys in 2011 and had MSK-IMPACT testing in 2015. Although his family history did not suggest it, his test results showed he had a condition called Lynch syndrome. Also known as hereditary nonpolyposis colorectal cancer, Lynch syndrome is associated with a genetic predisposition to a number of different cancer types. It's most commonly linked to colon and rectal cancers, but it's also known to increase the risk of developing uterine, urothelial, and ovarian cancers, as well as other gastrointestinal cancers, such as tumors in the stomach, small intestine, and pancreas.

His doctors made this diagnosis because, in addition to flagging cancer-causing mutations in tumors, MSK-IMPACT provides extensive information about a patient's normal DNA. Clinical geneticists use this information to uncover which genetic changes were inherited by a person at birth and increase the risk of developing cancer and which developed over time within the cancer cell. Cancer-causing genes that are inherited are likely to be shared by brothers, sisters, and children, as well as parents.

MSK's specialists are uniquely experienced in interpreting these clues. People who harbor these genetic alterations can undergo genetic counseling and learn about what these findings mean. Their family members are also offered the opportunity to undergo genetic testing and counseling.

> "Once I knew, it was important to me that my family have testing too, just in case they had the same condition."
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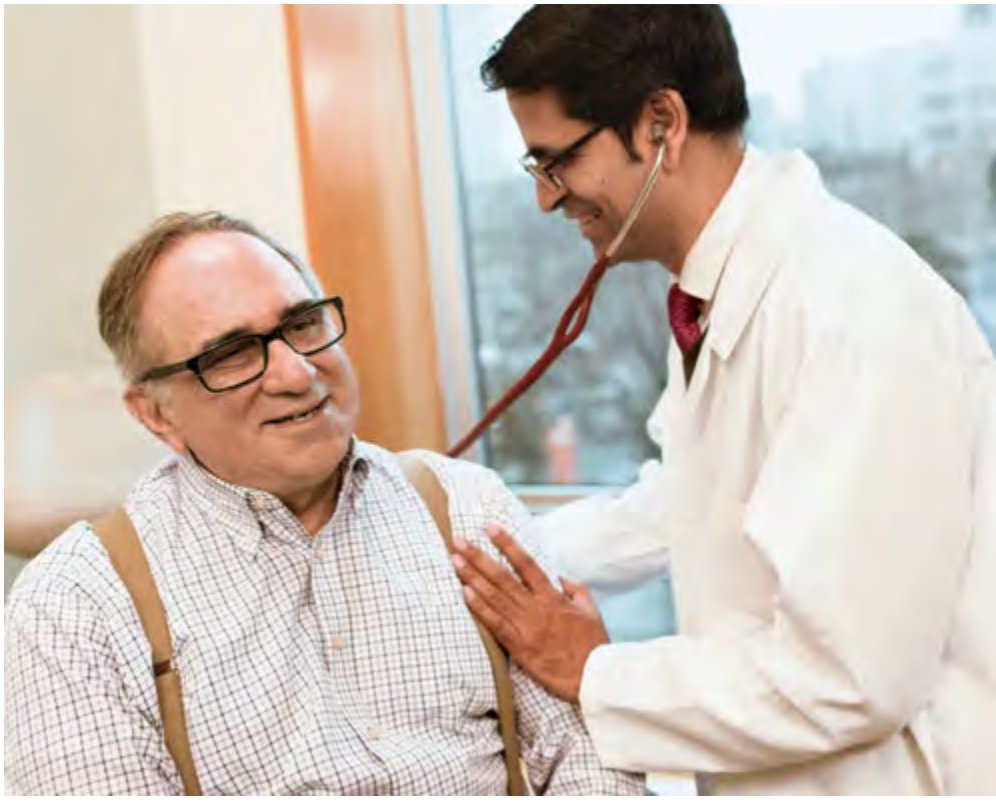
> –MITCHELL KATZ



After Mr. Katz learned he had Lynch syndrome in 2015, he met with MSK genetic counselor Meg Sheehan, who explained the risks to him and recommended that other family members get tested. "I was very surprised to find out I had this mutation because I didn't have a strong family history of cancer," he says. "Once I knew, it was important to me that my family have testing too, just in case they had the same condition."

Ultimately, his daughters, Stacy, 34, and Shana, 29, were found to carry the same mutation, as well as his older brother, Elliot, 66. All four of them, including Mr. Katz, who is still at risk of developing additional cancers, began undergoing regular colonoscopy screenings to check for the presence of colorectal cancer, an action they never would have known to take otherwise.

In February 2018, Elliot Katz was found to have an early-stage colorectal cancer, thanks to a colonoscopy. In April 2018, MSK surgeon José Guillem performed surgery to remove the tumor and a portion of his colon.

Mitchell Katz was already enrolled in a clinical trial for the immunotherapy drug atezolizumab (Tecentriq®) when he found out that his urothelial cancer had an excess number of mutations due to his underlying Lynch syndrome. It turned out that people with mutations in Lynch syndrome–associated genes were among those in the trial whose cancers responded best to the immunotherapy. Mr. Katz continues to see MSK medical oncologist Gopa Iyer for his treatment and has had no evidence of disease in the nearly four years since he started receiving the drug.

Top: Mitchell Katz and his doctor Gopa Iyer. *Above*: Mr. Katz (*right*) and his brother, Elliot, were both found to have Lynch syndrome.

FAMILY MATTERS

For a long time, experts thought that only 5 to 10 percent of cancers were triggered in part by a hereditary component. But as a result of MSK-IMPACT, they're realizing that the inherited risk may be substantially higher for some people, particularly those with advanced cancer. They're also finding that inherited factors may play a role in a much greater variety of cancer types.

"At the time a person is diagnosed with advanced cancer, we have a vital opportunity to conduct comprehensive genetic testing," says Kenneth Offit, Chief of the Clinical Genetics Service and head of the Robert and Kate Niehaus Center for Inherited Cancer Genomics. The Niehaus Center, working closely with molecular pathologists Diana Mandelker and Liying Zhang, aims to use hereditary genomic data to develop new approaches for cancer prevention, early detection, and treatment for families with these inherited risks.

"By learning about the presence of inherited mutations, we can set the stage for providing genetic counseling to families. That in turn can lead to better screening and prevention," says Dr. Offit. "No other institution is doing tests that compare tumor and normal tissues and family notification to the same degree as MSK."

A study published in September 2017 in the *Journal of the American Medical Association* (*JAMA*) and led by Dr. Offit's team found that 17.5 percent of those with advanced cancer had inherited cancer-causing mutations, and half of those people would not have been screened for those mutations based on their personal or family history alone.

Like Mr. Katz, the other people in the *JAMA* study who were found to have inherited mutations in cancer-causing genes were invited to participate in counseling, along with their families. Family members then had the opportunity to undergo genetic testing as well.

Going forward, MSK hopes to expand tumor sequencing to even more people. "This new technology has enabled our doctors to extend the promise of precision medicine to many people, including those with common or rare tumor types," Dr. Klimstra says. ■

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>
> –KENNETH OFFIT

Top: In addition to consulting with adult patients and their families, Meg Sheehan also works with families of children who have cancer. *Above*: Kenneth Offit (*left*) and genetic counselor Yelena Kemel have found that inherited cancer mutations are more common than expected in people who have advanced cancer.