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MSK-IMPACT Tumor Profiling Test Authorized by FDA

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A tumor profiling assay that tests for far more mutations than any other test has received authorization from the US Food and Drug Administration (FDA).

The product, developed at the Memorial Sloan Kettering (MSK) Cancer Center in New York City, is known as *MSK-IMPACT* (MSK-Integrated Mutation Profiling of Actionable Cancer Targets).

It uses next-generation sequencing (NGS) to identify mutations in 468 unique genes, as well as other molecular changes in the genomic makeup of a person's tumor. Identifying actionable mutations in tumor tissue offers the hope of precision medicine — treatment that targets the specific mutation that has been found.

"Pathology guides almost every decision point in the cancer treatment process, and MSK-IMPACT has enabled our pathologists to provide a better understanding of the genetic underpinnings of each patient's illness," commented David Klimstra, MD, chair of the Department of Pathology and James Ewing Alumni Chair of Pathology at MSK.

"The valuable data obtained through the sequencing can guide treatment choices and, in some cases, identify patients who are candidates for a cancer clinical trial," Dr Klimstra said in an MSK statement.

"While clinical trials are vital to developing and improving treatments, only 4% of all patients enroll in cancer clinical trials each year. MSK-IMPACT is designed to address this problem," said test developer Michael Berger, PhD, associate director of the Marie-Josée and Henry R. Kravis Center for Molecular Oncology and assistant attending molecular geneticist in the Department of Pathology at MSK.

"MSK-IMPACT has helped doctors accelerate the enrollment of patients into cancer clinical trials, potentially leading to earlier approval of new therapies," he added.

"NGS technologies can examine hundreds, if not millions, of DNA variants at a time; and we are only at the beginning of realizing the true potential for these devices to assist patients and their health care providers in learning about the genetic underpinnings of their disease," commented Jeffrey Shuren, MD, director of the FDA's Center for Devices and Radiological Health, in a statement released by the agency.

New Approval Pathway for Such Tests

MSK-IMPACT becomes the first tumor-profiling in vitro laboratory diagnostic test to receive authorization through the FDA.

In its statement, the agency said that this product's ability to detect genetic mutations (analytical performance) was evaluated for precision, accuracy, and limit of detection. Results indicated that the assay is highly accurate (>99%) and capable of detecting a mutation at a frequency of approximately 5% (range, 2% to 5%). Additionally, detection of certain molecular changes (microsatellite instability) using MSK-IMPACT was concordant more than 92% of the time across multiple cancer types in 175 cases when compared with traditional methods of detection.

The FDA reviewed the test through the de novo premarket review pathway, a regulatory pathway for some low- to moderate-risk devices that are novel and for which there is no legally marketed device (predicate device). As part of the data that it submitted for approval, MSK included information that it had previously submitted to the New York State Department of Health (NYSDOH), which had conducted its own review and approved it for use on samples coming from patients in the state of New York.

The outcome of all of this is a new streamlined pathway for authorization of such tests in the future.

The FDA announced that it has recently accredited the NYSDOH as an FDA third-party reviewer of all in vitro diagnostics, which include tests such as MSK-IMPACT. In practice this means that if an NGS-based tumor profiling test has been approved by NYSDOH, the laboratory that received this approval no longer needs to submit a separate 510(k) application to the FDA as well.

"The goal of allowing NGS-based tumor profiling tests to undergo review by accredited third parties is to reduce the burden on test developers and streamline the regulatory assessment of these types of innovative products," said FDA Commissioner

Scott Gottlieb, MD, in a statement. "As this field advances, we are modernizing the FDA's approach to the efficient authorization of laboratory tests from developers that voluntarily seek 510(k) clearance," he added.

"This is another example of where the FDA is working to find creative and flexible approaches to regulation that spurs development and efficient delivery of innovative technology," he commented.

MSK-IMPACT Test

The MSK-IMPACT test uses NGS of formalin-fixed, paraffin-embedded tumor tissue and matched normal tissue from patients with a wide range of solid tumors to detect genetic alterations with the multigene panel. It is a single-site assay done in diagnostic molecular pathology laboratories at MSK.

"To date, more than 20,000 MSK patients with advanced cancers have had their tumors sequenced through MSK-IMPACT, and the resulting data have helped guide therapy while providing a wealth of new information about the genomic features of both common and rare cancer types," according to the MSK statement. However, the statement also adds that the test results are "not conclusive or prescriptive for labeled use of any specific product."

Details of the test were first published earlier this year in *Nature Medicine.* Using this test in over 10,000 patients, the MSK researchers found that this in vitro diagnostic test identified actionable mutations in 37% of patients — mutations that could be matched to targeted agents available in a clinical trial or as standard of care. Of these patients, 11% were enrolled in genomically matched clinical trials. In addition, some of the mutations in DNA mismatch repair genes, which result in microsatellite instability, now have approved immunotherapies to treat this defect.

"The breadth and depth of MSK-IMPACT has allowed MSK researchers to detect important genomic alterations that would have been missed by other approaches," MSK's David Solit, MD, director of the Marie-Josée and Henry R. Kravis Center for Molecular Oncology, said in a statement.

In a subsequent study reported by *Medscape Medical News*, the MSK-IMPACT test detected more inherited cancer gene mutations compared with traditional methods (ie, phenotypic testing) based on family history, age, and tumor type. The MSK researchers indicated that germline testing across all patients with cancer can create a vital opportunity for precision prevention to treat cancer preemptively in the next generation through increased surveillance or risk-reducing surgical procedures. "Determining germline mutations allows for targeted treatment for patients and precision prevention for families," lead researcher, Kenneth Offit, MD, told *Medscape Medical News*.

Also important is that data collected through MSK-IMPACT testing are being made available to the larger scientific community through cBioPortal, a database developed at MSK. While the patient remains anonymous, basic clinical data are made available. This allows researchers to determine the link between a particular genetic alteration and patient outcomes.

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