MSK-IMPACT: A Comprehensive Tumor Sequencing Test to Detect Targetable DNA Mutations

Research technician Hun Jae Jung works in the sequencing lab on a NOVASeq 600 sequencer.

What Is MSK-IMPACT?

MSK-IMPACT® (Integrated Mutation Profiling of Actionable Cancer Targets) is a targeted tumor-sequencing test available to patients at Memorial Sloan Kettering Cancer Center (MSK). It is used to detect mutations and other critical changes in the genes of both rare and common cancers. MSK-IMPACT can be used on any solid tumor, no matter where in the body the cancer started.

With the MSK-IMPACT test, doctors can quickly find out whether a tumor has changes that make the cancer vulnerable to particular drugs. MSK patients can then be matched to the available therapies or clinical trials that are most likely to benefit them. MSK-IMPACT can also detect inherited genetic variants that can explain how a patient's cancer may have started and provide insight into potential treatments and risks of new cancers.

MSK-IMPACT was developed and validated by scientists in the Department of Pathology's Molecular Diagnostics Service and the Marie-Josée and Henry R. Kravis Center for Molecular Oncology (CMO). The test uses cutting-edge next-generation DNA-sequencing technology. It can detect many classes of genomic changes. These include mutations, gene amplifications, and gene deletions, as well as genomic rearrangements and signatures such as microsatellite instability and tumor mutation burden. The test provides a comprehensive picture of the full spectrum of genetic changes in a tumor.

How Does MSK-IMPACT Work?

MSK-IMPACT is a tumor sequencing test that directly compares patient DNA from their tumor cells to DNA from their normal tissue using a high-throughput, targeted DNA sequencing. The panel is comprised of 505 genes. These genes were selected by scientific and clinical researchers from across MSK because they play a critical role in the development and behavior of tumors. All actionable targets (genes that provide important information about the disease and possibly can be targeted with drugs) are included. MSK-IMPACT is updated regularly as new targets are discovered.

VIDEO | 05:30

Learn More About the Molecular Diagnostics Service at MSK

Go inside the molecular pathology lab, located on the fourth floor of the Arnold and Maria Schwartz Cancer Research Building at MSK. This is where tumor-sequencing tests MSK-IMPACT® and MSK-ACCESS® take place. These tests can help doctors learn important information about individual people's cancers and help guide their treatment.
Video Details (https://www.mskcc.org/videos/learn-more-about-molecular-diagnostics-service-msk)

MSK-IMPACT uses hybridization capture and next-generation sequencing to identify tumor-specific genomic alterations in all exons of all targeted genes. The alterations it detects include single-nucleotide variants, small insertion and deletions, copy number alterations, chromosomal rearrangements, tumor mutation burden, and microsatellite instability.

A companion test for people with blood cancer (leukemias and lymphomas), MSK-IMPACT Heme, has also been validated and is in use. That test evaluates 468 genes. Many of them are the same genes that are included for solid tumors.

MSK-IMPACT is the first next-generation sequencing tumor profiling test (academic or commercial) to receive approval from the New York State Department of Health and U.S. Food and Drug Administration class II authorization.

MSK-IMPACT in Clinical Care

Clinical MSK-IMPACT testing is performed in the Diagnostic Molecular Pathology Laboratory in the Department of Pathology and Laboratory Medicine. This lab is CLIA (Clinical Laboratory Improvement Amendments) compliant and is jointly led by the Molecular Diagnostics Service and the Clinical Computational Diagnostics Service. MSK-IMPACT test results are reported in each patient's electronic medical record and accessible through the cBioPortal for Cancer Genomics.

To take full advantage of MSK-IMPACT, MSK doctors and researchers developed a knowledge base called OncoKB®. This system includes information about the clinical and biological effects of thousands of genomic changes. That information is based on regulatory approvals, clinical trial databases, scientific literature, and clinical guidelines. Using OncoKB, doctors can select the best therapies for each patient based on their tumor's genomic profile.

MSK-IMPACT results are also used to match patients to the most appropriate clinical trials involving new drugs that can target molecular alterations in their tumor. By identifying patients that are most likely to respond to investigational treatments, this can give new drugs the best chance of getting approved.

These clinical trials include studies focusing on patients that all have the same kind of cancer (for example, breast cancer, lung cancer, or prostate cancer). They also include studies involving patients across all types of cancer that all have the same or similar mutations. The latter studies, called basket trials, are designed to allow for patients with common and rare cancer types to access molecularly targeted therapies more quickly. They are primarily conducted in partnership with MSK's Early Drug Development Service.

A notable feature of MSK-IMPACT is that two DNA samples from each person are sequenced and compared: DNA from tumor tissue and from normal tissue. The normal tissue is usually a sample of white blood cells. Directly comparing the tumor's genome to the genome in normal blood ensures that

the mutations detected by MSK-IMPACT are specific to the cancer cells.

What's more, looking at normal genomes can show whether there are any inherited genetic mutations associated with an increased risk of cancer. When these mutations are found, patients and their families are referred to the Clinical Genetics Service . The service provides both screening and counseling. Research into the function of inherited mutations is being done through the Robert and Kate Niehaus Center for Inherited Cancer Genomics.

MSK-IMPACT may also reveal mutations in blood cells associated with clonal hematopoiesis . These mutations are more common in older people. They may lead to an increased risk of a secondary blood cancer or cardiovascular disease. To monitor people with clonal hematopoiesis for early detection of these adverse health effects, MSK established the first clonal hematopoiesis clinic in 2018.

MSK-IMPACT in Research

MSK-IMPACT is also used as a research test in the CMO to look at samples that are retrospectively collected for research purposes. These results may not be returned to patients, but they inform research advances and discoveries made by MSK investigators.

An important goal of MSK-IMPACT is to gather data and share analyses within MSK and with the public. The data gathered is being used to develop smarter cancer therapies. MSK-IMPACT results that have been stripped of all patient-identifying information are available for scientific use by everyone at MSK through the cBioPortal. This important resource facilitates critical scientific and clinical advances at MSK.

MSK-IMPACT results are also shared more broadly with the wider scientific community through AACR Project GENIE . Through this American Association for Cancer Research consortium, MSK-IMPACT data can be aggregated with tumor-sequencing data from other institutions, which is especially valuable for studying rare cancer types and infrequently mutated genes.

MSK-IMPACT in Publications

As of the end of 2024, more than 1,000 peer-reviewed scientific publications by MSK authors have featured results from clinical MSK-IMPACT testing. A partial list of selected key papers is shown below.

Multiple Cancer Types

- Arora K, Suehnholz SP, Zhang H, et al. Genetic Ancestry-Based Differences in Biomarker-Based Eligibility for Precision Oncology Therapies . *JAMA Oncol*. 2025 Mar 1;11(3):310-316. doi: 10.1001/jamaoncol.2024.5794.
- Zucker M, Perry MA, Gould SI, et al. Pan-cancer analysis of biallelic inactivation in tumor suppressor genes identifies KEAP1 zygosity as a predictive biomarker in lung cancer . *Cell*. 2025 Feb 6;188(3):851-867.e17. doi: 10.1016/j.cell.2024.11.010. Epub 2024 Dec 18.
- Ziegler J, Hechtman JF, Rana S, et al. A deep multiple instance learning framework improves microsatellite instability detection from tumor next generation sequencing . *Nat Commun*. 2025 Jan 2;16(1):136. doi: 10.1038/s41467-024-54970-z.
- Gormally MV, Chen MF, Noronha AM, et al. Next-Generation Sequencing for HLA Genotype Screening and Matching to HLA-Restricted Therapies . *JAMA Oncol*. 2025 Jan 1;11(1):74-76. doi: 10.1001/jamaoncol.2024.5364.
- Jee J, Fong C, Pichotta K, et al. Automated real-world data integration improves cancer outcome prediction. *Nature*. 2024 Dec;636(8043):728-736. doi: 10.1038/s41586-024-08167-5. Epub 2024 Nov 6.
- Suehnholz SP, Nissan MH, Zhang H, et al. Quantifying the Expanding Landscape of Clinical Actionability for Patients with Cancer. *Cancer Discov*. 2024 Jan 12;14(1):49-65. doi: 10.1158/2159-8290.CD-23-0467.
- Nguyen B, Fong C, Luthra A, et al. Genomic characterization of metastatic patterns from prospective clinical sequencing of 25,000 patients. *Cell*. 2022 Feb 3;185(3):563-575.e11. doi: 10.1016/j.cell.2022.01.003.
- Srinivasan P, Bandlamudi C, Jonsson P, et al. The context-specific role of germline pathogenicity in tumorigenesis. *Nat Genet*. 2021 Nov;53(11):1577-1585. doi: 10.1038/s41588-021-00949-1. Epub 2021 Nov 5.
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- Tsui DWY, Cheng ML, Shady M, et al. Tumor fraction-guided cell-free DNA profiling in metastatic solid tumor patients . *Genome Med*. 2021 May 31;13(1):96. doi: 10.1186/s13073-021-00898-8.
- Gorelick AN, Sánchez-Rivera FJ, Cai Y, et al. Phase and context shape the function of composite oncogenic mutations. *Nature*. 2020 Jun;582(7810):100-103. doi: 10.1038/s41586-020-2315-8. Epub 2020 May 27.
- Penson A, Camacho N, Zheng Y, et al. Development of Genome-Derived Tumor Type Prediction to Inform Clinical Cancer Care. *JAMA Oncol*.

2020 Jan 1;6(1):84-91. doi: 10.1001/jamaoncol.2019.3985.

- Jonsson P, Bandlamudi C, Cheng ML, et al. Tumour lineage shapes BRCA-mediated phenotypes. *Nature*. 2019 Jul;571(7766):576-579. doi: 10.1038/s41586-019-1382-1. Epub 2019 Jul 10. Erratum in: *Nature*. 2020 Jan;577(7789):E1. doi: 10.1038/s41586-019-1839-2.
- Latham A, Srinivasan P, Kemel Y, et al. Microsatellite instability is associated with the presence of Lynch syndrome pan-cancer . *J Clin Oncol*. 2019 Feb 1;37(4):286-295. doi: 10.1200/JCO.18.00283. Epub 2018 Oct 30.
- Samstein RM, Lee CH, Shoushtari AN, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet*. 2019 Feb;51(2):202-206. doi: 10.1038/s41588-018-0312-8. Epub 2019 Jan 14.
- Bielski CM, Donoghue MTA, Gadiya M, et al. Widespread selection for oncogenic mutant allele imbalance in cancer . *Cancer Cell*. 2018 Nov 12;34(5):852-862.e4. doi: 10.1016/j.ccell.2018.10.003. Epub 2018 Nov 1.
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- Coombs CC, Zehir A, Devlin SM, et al. Therapy-related clonal hematopoiesis in patients with nonhematologic cancers is common and associated with adverse clinical outcomes . *Cell Stem Cell*. 2017 Sep 7;21(3):374-382.e4. doi: 10.1016/j.stem.2017.07.010. Epub 2017 Aug 10.
- Mandelker D, Zhang L, Kemel Y, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs. guideline-based germline testing . *JAMA*. 2017 Sep 5;318(9):825-835. doi: 10.1001/jama.2017.11137.
- André F, Arnedos M, Baras AS, et al. AACR Project GENIE: powering precision medicine through an international consortium. *Cancer Discov*. 2017 Aug;7(8):818-831. doi: 10.1158/2159-8290.CD-17-0151. Epub 2017 Jun 1.
- Zehir A, Benayed R, Shah RH, et al Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients . *Nat Med*. 2017 Jun;23(6):703-713. doi: 10.1038/nm.4333. Epub 2017 May 8.

Individual Cancer Types

- Varghese AM, Perry MA, Chou JF, et al. Clinicogenomic landscape of pancreatic adenocarcinoma identifies KRAS mutant dosage as prognostic of overall survival. *Nat Med*. 2025 Feb;31(2):466-477. doi: 10.1038/s41591-024-03362-3. Epub 2025 Jan 3.
- Rekhtman N, Tischfield SE, Febres-Aldana CA, et al. Chromothripsis-Mediated Small Cell Lung Carcinoma. *Cancer Discov*. 2025 Jan 13;15(1):83-104. doi: 10.1158/2159-8290.CD-24-0286.
- Chatila WK, Kim JK, Walch H, et al. Genomic and transcriptomic determinants of response to neoadjuvant therapy in rectal cancer. *Nat Med*. 2022 Aug;28(8):1646-1655. doi: 10.1038/s41591-022-01930-z. Epub 2022 Aug 15.
- Harding JJ, Nandakumar S, Armenia J, et al. Prospective genotyping of hepatocellular carcinoma: clinical implications of next generation sequencing for matching patients to targeted and immune therapies . *Clin Cancer Res*. 2019 Apr 1;25(7):2116-2126. doi: 10.1158/1078-0432.CCR-18-2293. Epub 2018 Oct 29.
- Miller AM, Shah RH, Pentsova EI, et al. Tracking tumour evolution in glioma through liquid biopsies of cerebrospinal fluid . *Nature*. 2019 Jan;565(7741):654-658. doi: 10.1038/s41586-019-0882-3. Epub 2019 Jan 23.
- Soumerai TE, Donoghue MTA, Bandlamudi C, et al. Clinical utility of prospective molecular characterization in advanced endometrial cancer . *Clin Cancer Res*. 2018 Dec 1;24(23):5939-5947. doi: 10.1158/1078-0432.CCR-18-0412. Epub 2018 Aug 1.
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