The Food and Drug Administration (FDA) issued a final order on June 22, 2018, Classification of the Next Generation Sequencing Based Tumor Profiling Test [10], that classified [11] next generation sequencing (NGS) tumor profiling tests as Class II devices. The first of these devices, the Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) test was developed by Memorial Sloan-Kettering Cancer Center’s Department of Pathology. The FDA final ruling applies to both the MSK-IMPACT test specifically and NGS tumor profiling tests broadly.

This classification of devices can enter the market without having to be approved by the FDA, but must send in certain premarket notification submissions to ensure that the devices are safe and effective (21 U.S.C. 360 [12](c)(a)(1)(B)). With a Class II designation, the FDA requires some additional safety measures, or special controls, for the marketing and use of these devices to provide safety and efficacy assurances. These devices were codified into the Code of Federal Regulations under Immunology and Microbiology Devices (21 CFR 866.6080 [13]).

In the final order, the FDA specifically focuses on two health risks associated with the MSK-IMPACT test: false positives
or false negatives as a result of incorrect test performance, and the incorrect interpretation of test results. To address these health concerns, the FDA specifies that additional safety measures are required for these NGS tests; these special controls require that a company submit a notification to the FDA before they enter the market. The special controls include providing a summary of the genes that will be tested, a list of who can use the device and what samples can be tested, the descriptions and specifications for the device, explanations of each step of the testing process, and the links to the information given to the user and used by the device.

Context

Next generation sequencing[14] allows scientists to cheaply and rapidly analyze an organism’s entire genetic makeup. To put this into context, in 1990, the Human Genome Project[15], an international effort to sequence a complete set of DNA in the human body, took ten years and cost almost three billion dollars. NGS can sequence[16] a person’s genetic makeup in a single day for less than five thousand dollars.

NGS diagnostic tests use a myriad of new technologies[17] — including devices for both clinical and research settings — to search through a person’s entire genetic makeup for mutations correlated with disease. The FDA notes[18] that this technology could help improve treatment for patients with genetic disease by personalizing their treatment based on their specific genetic mutation. NGS is leading to a wave of new diagnostic tools, such as the NGS tumor profiling test, that could help researchers better understand disease in the hope of improving patients’ treatment. With the development of NGS tumor profiling tests, the FDA had to determine if the tools were scientifically valid and create the necessary regulatory pathways to ensure their safety and efficacy without stifling access to a potentially life-saving technology.

In April 2018, the FDA finalized two guidances[19] relating to the development of NGS tests for clinical purposes. The first guidance, Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics[20] (SciPol Full Brief[21]), provides the FDA’s thinking on using public databases to bolster clinical claims for a diagnostic device. The second guidance, Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases[22], focuses specifically on the development and validation of NGS tests for individuals with a genetic disease.

Policy History

On September 27, 2017, Memorial Sloan-Kettering Cancer Center Department of Pathology sent a request to the FDA to take their NGS tumor profiling test, the MSK–IMPACT, to market without FDA approval. The FDA reviewed their request and on November 17, 2017, they approved it by issuing a broad ruling to Memorial Sloan-Kettering Cancer Center regarding all NGS tumor profiling tests. On June 22, 2018, the FDA issued a final order, publicly declaring their decision.

The Science

Science Synopsis

Molecular profiling of tumors[23] has become a standard technique for classifying tumors. Molecular profiling allows oncologists to collect information about the molecular and genetic makeup of a tumor, which in turn informs clinicians and doctors about the underlying cancer. Next generation sequencing techniques, which have begun to replace traditional methods of molecular profiling, offer the unique ability to scan a person’s entire genome in search of specific cancer-causing mutations. Specifically, NGS tumor profiling tests scan tissue samples from a tumor to detect genetic mutations associated with specific variants of cancers. Clinicians hope that these genetic variants will provide information to help doctors better understand and treat their patients.

Next generation sequencing techniques vastly improved the speed and cost[16] of sequencing entire genomes. Rather
than decoding a strand of DNA from start to finish like traditional sequencing techniques, NGS techniques break up long strands of DNA into multiple shorter strands. These short strands are then analyzed simultaneously through a computer-automated process. As such, they can be used to analyze dozens or even hundreds of genes simultaneously as compared to more traditional methods, which are both slower and costlier.

Next generation sequencing techniques allow for more targeted approaches [24] to cancer treatments. By finding specific, cancer-causing genetic mutations, oncologists can more specifically classify tumors and provide targeted treatments based on a patient’s specific tumor. One review, Next-Generation Sequencing in Oncology: Genetic Diagnosis, Risk Prediction and Cancer Classification [25], provides an in-depth explanation of NGS based tumor profiling tests and how they can be used to improve treatments. The authors specifically profile a few NGS tests used in clinical settings, including the analysis of cancer somatic mutations and using DNA sequencing to identify inherited cancer biomarkers. For example, the authors discuss hereditary breast and ovarian cancer — with the highly profiled and penetrant BRCA1 and BRCA2 genes — as having additional moderate-risk genetic variants associated with risk of developing the cancer. More traditional genetic screening would not have the capability to detect these moderate-risk variants, making the argument for the incorporation of NGS tests in clinical genetic screening.

MSK-IMPACT [26] is a diagnostic test that utilizes NGS to find genetic mutations of both rare and common cancers. As described by Memorial Sloan Kettering, MSK-IMPACT is designed to give doctors quick information about a tumor to inform the treatment options – specifically, whether the cancer is more or less likely to be vulnerable to certain drugs. The diagnostic test works through analyzing 468 genes that were chosen because of their demonstrated role in tumor biology. After administering the test and analyzing for genetic mutations, clinicians can use a database, OncoKB [27], to understand how an individual tumor’s genetic changes contribute to biological traits that will ultimately inform the potential course of treatment.

The Debate

Scientific Controversies / Uncertainties

Researchers dispute whether NGS based tumor profiling tests are accurate and informative enough to be used in a clinical setting. Previously, cancer researchers expressed concern [28] that the tests are not accurate enough to be used outside of research. Other groups of researchers have determined that the technology is accurate and gives useful insight that can be used to improve health outcomes [29] in cancer patients.

Endorsements & Opposition

- David Klimstra, Memorial Sloan Kettering’s Department of Pathology Chair, blog [30], June 12, 2014: “[MSK-IMPACT is] an incredibly powerful test,”
- Dr. Jeffrey Shuren, M.D., Director of the FDA’s Center for Devices and Radiological Health press release [31], November 15, 2017: “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,”
- Kathleen Harden and Kimberly Blackwell, breast cancer genetics specialist, academic journal article [32], August 12, 2014: “Although many of the therapeutic implications of NGS involve clinical trial participation, NGS is ready for the clinic.”
- Michael Berger, developer of MSK-IMPACT, blog [30], June 12, 2014: “[Using MSK-IMPACT] ... we are able to look at hundreds of genes in multiple patients simultaneously and collect an enormous amount of information about each of these genes,”
- Mark Robson, clinical genetics specialist, academic journal article [33], August 12, 2014: “Somatic mutation profiling by NGS is not necessary for deployment of approved genomically-directed treatments and is not yet at the point where it can be used to direct off-protocol treatment.”
- Dr. Scott Gottlieb, M.D., FDA Commissioner, press release [31], November 15, 2017: “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. We’ll continue to look for opportunities to create regulatory efficiencies where possible to drive broader access to tools that improve American health, while maintaining the safety and efficacy standards that patients should expect from their FDA-reviewed products.”

**Potential Impacts**

Approval and classification of the MSK-IMPACT test for clinical use fits into a broader picture of FDA drug and device approvals [34] to advance precision medicine. In this final approval, the FDA also set a broad classification for subsequent NGS tumor diagnostic tests, which will require special controls to ensure safety and efficacy. In this approval, the FDA considered three levels of biomarkers [35] to inform tumor profiling NGS tests: companion diagnostics, cancer mutations with evidence of clinical significance, and cancer mutations with potential clinical significance. Some believe that this integration of NGS diagnostic tests in oncology will impact the future of cancer diagnosis and treatment in a variety of ways.

Illumina, a company that specializes in genetic sequencing and molecular diagnosis, predicts [36] that NGS diagnostic tests will bring a more personalized and accurate look into the molecular changes of individual tumors. In this statement, Illumina also suggests that these diagnostic tools will change the way that tumors and cancers are treated by providing more selective treatment options. These statements are supported by a paper analyzing the use of NGS tests [37] to inform clinical treatment decisions; the authors found that, between February and May 2017, 63% of oncologists used NGS tests as a part of their decision of how to treat tumors, and 36% of oncologists “often” used these tests in guiding their decision-making.

One question that often accompanies new medical diagnostic tests or treatments is how insurers will cover these new, often costly, clinical tools. In March 2018, the Centers for Medicare and Medicaid Services announced [38] that Medicare would cover some NGS tests for patients with advanced cancer. This announcement was made with the concurrent approval of the FoundationOne CDx test [39] in November 2017, a NGS in vitro diagnostic test that surveys 324 genes to find genetic mutations in a solid tumor. In 2018, the FoundationOne CDx diagnostic test was estimated to cost $5,800 [40] per patient.

**Status**

The FDA issued the final order on June 22, 2018.

**Recommended Citation**


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