Tumor mutation burden (TMB) as biomarker in cancer: Scientists assess the performance of six genetic tests

The number of acquired changes in the genetic material of tumor tissue, the so-called tumor mutation burden (TMB), is used by oncologists as a biomarker to predict which patients could benefit from immunotherapy. There are now a variety of tests on the market allowing scientists to draw conclusions about TMB by analyzing several hundred genes. Scientists have now evaluated six genetic tests for reliability and have demonstrated that these multi-gene panels are suitable for use in routine clinical diagnostics.

Immune checkpoint inhibitors are an important treatment option for advanced cancers. Individual patient groups respond very differently to immunotherapy despite having the same diagnosis. Biomarkers can help make better predictions for the course of therapy. The number of acquired mutations in the genetic material of the tumor cell, the so-called tumor mutation burden (TMB) is one such biomarker. The greater the number of acquired genetic changes found in a tumor, the higher the likelihood that the body’s immune defense will be activated and new active substances, such as the so-called checkpoint inhibitors, will work.

Two methods are currently used to determine the TMB in tumor tissue: Exome sequencing - also called whole exome sequencing (WES) - decodes all of the approximately 20,000 genes that code for the protein molecules in a cell. "The WES analysis provides us with very precise and reliable data, which can form the basis for recommendations for therapy. However, with an analysis time of three to four weeks, the procedure is relatively slow and therefore not yet suitable for routine clinical diagnostics. Furthermore, very small tissue samples are sometimes difficult to analyze using WES, “explains Stefan Fröhling, Managing Director at National Center for Tumor Diseases (NCT) Heidelberg and Head of the Department of Translational Medical Oncology at the German Cancer Research Center (DKFZ).

A gene panel study is able to analyze several hundred genes in a shorter time frame. The method allows researchers to estimate the mutation load in the tumor tissue based on the examination of gene segments. This method is also less expensive as, in contrast to the WES analysis, no fresh tumor material is required. In fact the examination can be carried out on paraffin-embedded tissue sections generally used during diagnosis and available to pathologists. Tumor DNA from the patient's blood has even been recently used for multi-gene analysis.

Currently, several genetic tests which can be used to determine TMB are available. "However, a detailed assessment of the overall performance of these TMB tests is so far lacking. We therefore asked ourselves, to what extent the results of..."
the different tests, even across different institutions, are comparable. We were also interested in whether these methods provide the type of reliable information similar to exome sequencing and which factors influence the results,” reports Albrecht Stenzinger, head of the Molecular Pathology Center at the Institute of Pathology, Heidelberg University Hospital (UKHD) and scientist at the German Center for Lung Research (DZL).

In a current study, scientists from several universities in Germany and Switzerland, under the patronage of the Pathology Quality Assurance Initiative (QuiP), analyzed the performance and quality of six different genetic tests on 20 tumor samples and compared them with each other and with the accuracy of the WES method. The tissue samples from patients with lung cancer, head and neck tumors and colon cancer were tested more than 20 times with six gene panels and at 15 different institutions leading to over 450 data sets. With a parity of 87.7 percent, the results were highly comparable between the different panel tests and the centers. In 74.9 percent, test data for the TMB determination resulting from the gen-panel test matched the WES analyses.

The study showed that these gene panels can be used to approximate TMB, which in turn will allow us to select patients that will most likely benefit from immunotherapy. This makes it possible to better select patients who could benefit from immunotherapy. “Our study results are an important contribution to the evaluation of such genetic tests in routine clinical diagnostics,” says Matthias Schlesner, head of the junior research group bioinformatics and omics data at the DKFZ and scientist at the DZL. “However, we were also able to identify factors that influence the results of the genetic tests in daily practice. These include, for example, the number of tumor cells in the tissue section or the quality of the DNA. Further investigations will focus on controlling these factors and developing consistent methods for bioinformatics analysis,” adds Stenzinger.


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National Center for Tumor Diseases Heidelberg (NCT)
The National Center for Tumor Diseases (NCT) Heidelberg is a joint institution of the German Cancer Research Center, Heidelberg University Hospital (UKHD) and German Cancer Aid. The NCT’s goal is to link promising approaches from cancer research with patient care from diagnosis to treatment, aftercare and prevention. This is true for both diagnosis and treatment, follow-up care or prevention. The interdisciplinary tumor outpatient clinic is the central element of the NCT. Here, the patients benefit from an individual treatment plan prepared in interdisciplinary expert rounds, so-called tumor boards. Participation in clinical studies provides access to innovative therapies. The NCT thereby acts as a pioneering platform that translates novel research results from the laboratory into clinical practice. The NCT cooperates with self-help groups and supports them in their work. Since 2015, the NCT Heidelberg has maintained a partner site in Dresden. The Hopp Children’s Cancer Center (KiTZ) was established in Heidelberg in 2017. The pediatric oncologists at KiTZ work together in parallel structures with the NCT Heidelberg.

German Cancer Research Center (DKFZ)
The German Cancer Research Center (DKFZ) with its more than 3,000 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful.

The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Together with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are
translated into the clinic.
In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

Heidelberg University Hospital (UKHD)
Heidelberg University Hospital (UKHD) is one of the most important medical centers in Germany; Heidelberg University’s Medical Faculty is one of Europe’s most prestigious biomedical research facilities. Their shared objective is the development of innovative diagnostics and treatments and their prompt implementation for the benefit of the patient. The hospital and faculty employ approximately 13,000 individuals and are involved in training and qualification. Every year approximately 65,000 patients are treated as inpatients and 56,000 as day patients in more than 50 specialized clinical departments with around 2,000 beds, with more than 1 million patients being treated as outpatients. Together with the German Cancer Research Center and German Cancer Aid, the Heidelberg University Hospital established The National Center for Tumor Diseases (NCT) Heidelberg as the leading oncology center of excellence in Germany. The Heidelberg Curriculum Medicinale (HeiCuMed) is at the forefront of medical training in Germany. At present 3,700 aspiring physicians and doctors are studying in Heidelberg.

German Center for Lung Research (DZL)
The German Center for Lung Research (DZL e.V.) is an association of 29 leading university and non-university institutions dedicated to research into respiratory diseases. The DZL coordinates basic, disease- and patient-oriented research in the field of lung diseases and conducts it at the highest international level in order to accelerate the translation of basic scientific findings into new clinical concepts for improving patient care.

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