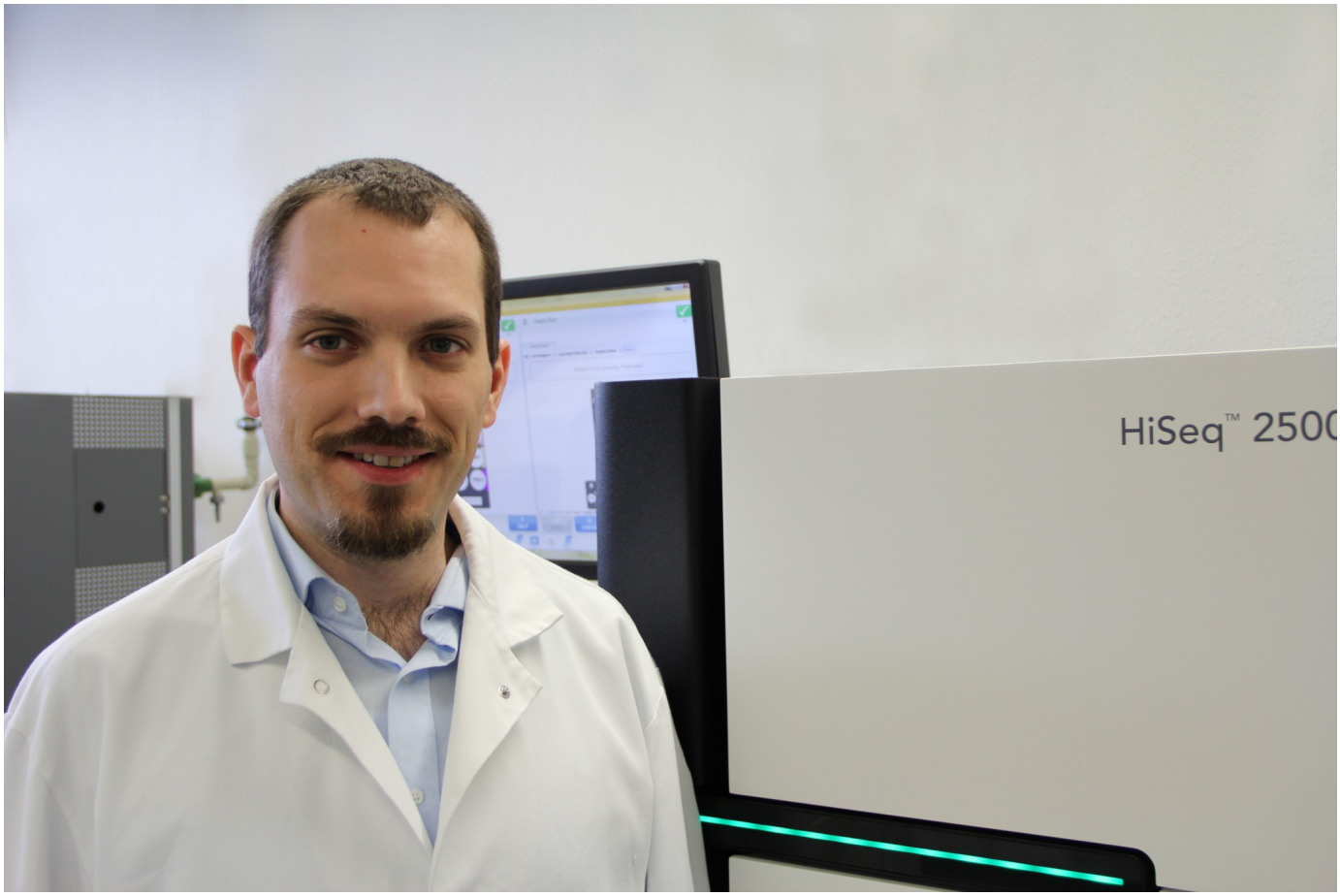
Healthcare industry BW

Personalised tumour diagnostics with high-throughput sequencing

CeGaT GmbH (Center for Genomics and Transcriptomics) in Tübingen is one of the first organisations that have managed to combine human genetic diagnostics with high-throughput sequencing for the diagnosis of specific tumour variants. CeGat researchers have developed diagnostic panels that they use to study more than 550 tumour-relevant genes simultaneously. The identification of genetic changes provides a more detailed diagnosis of tumours and helps doctors adapt therapy to the individual requirements of their cancer patients. The detailed diagnosis of tumours is an important step towards personalised patient treatment. It not only improves the chances of recovery, but also helps economise on healthcare costs by avoiding costly and stressful therapies to which patients may not respond.



Biochemist Dr. Moritz Menzel is in charge tumour diagnostics at CeGaT GmbH

Until recently, tumours were, if at all, only examined for the presence of a small number of frequent mutations using single-gene analyses. However, progress in high-throughput technologies now enables researchers to study a whole genome within a very short time and much more cheaply than with conventional methods. In 2010, CeGaT from Tübingen was among the first organisations to offer high-throughput sequencing services for the diagnosis of diseases. Starting off with a diagnostic sequencing panel for hereditary eye diseases, the company has also since developed panels for the diagnosis of tumours, enabling the identification of treatment-relevant mutations. Dr. Moritz Menzel, a tumour biologist in CeGaT's Panel Diagnostics team, sees this development as a breakthrough in clinical diagnostics.

Different tumour panels or the complete exome

CeGaT applies its panels to the diagnosis of many diseases. Each of the company's diagnostic panels contains a subset of genes that are very likely to be causative of a certain disease. Regular updates ensure that the panels always conform with the latest research. When the company began developing the tumour panels, it initially carried out comprehensive literature and sequence searches in standard databases to identify the genes involved in all important signalling and metabolic pathways as well as the genes associated with a significantly increased risk of developing malignomas. The sequences of these genes were used to create two tumour panels, one which integrates germline-related genes for the diagnosis of hereditary tumour syndromes and one which contains genes with somatic mutations that have an impact on tumour development. In addition to these two panels, doctors can also use CeGaT's exome sequencing services in order to identify all exonic somatic mutations.

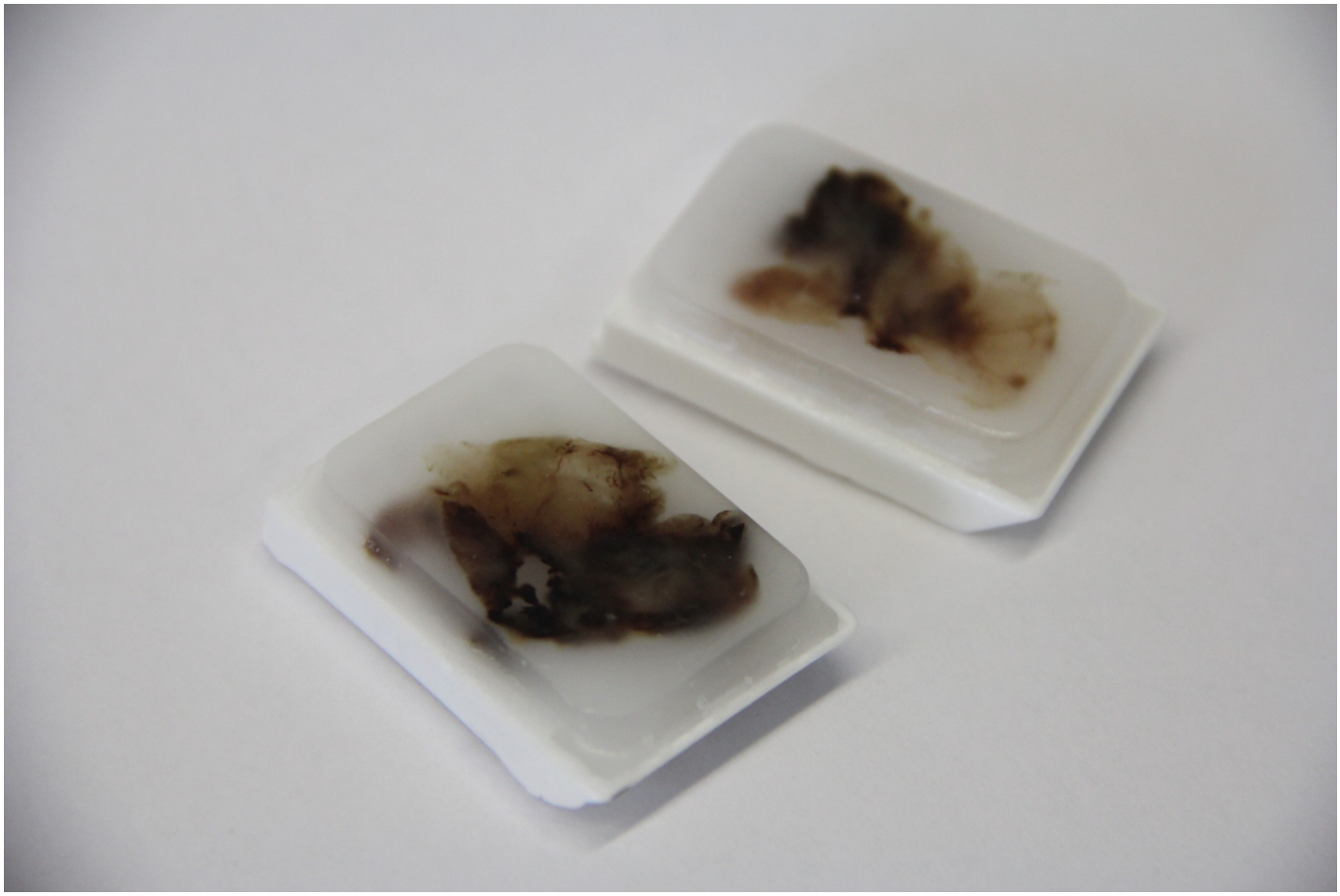
Early diagnosis of tumours with the germline panel

The germline tumour panel is designed for the diagnosis of hereditary tumour syndromes. It is used to study patients with a family history of a certain tumour. The identification of a specific mutation in the cancer-causing gene enables early diagnosis and therapy of the tumour, which considerably improves the treatment outcome. The germline panel can simultaneously analyse up to 97 genes associated with a significantly increased risk of developing malignomas. The analysis can be done with a few millilitres of blood taken from the patient from which the DNA is isolated. Subpanels comprising genes relevant for specific tumour syndromes are available, including for colorectal and breast cancer.

Individualised therapy following diagnosis with the somatic tumour panel

The second tumour panel is used for the analysis of somatic mutations in actual tumour samples. The somatic tumour panel comprises 551 genes with known mutations that can have an impact on tumour development. CeGaT's team of scientists and medical doctors analyses the sequencing data and prepares a medical report. "There is a growing number of drugs that are only effective in tumours characterised with specific gene mutations. On the other hand, some mutations can also make the tumour unresponsive to treatment with a specific drug. In addition, all tumour drugs are associated with strong adverse effects. Successful drug management of tumours relies on being able to select an appropriate drug, and exclude drugs that are likely to have the least effect," said Dr. Menzel.

The drug gefitinib, used for certain breast and lung cancers, is one such example. It is an EGFR (epidermal growth factor receptor) inhibitor that is only effective in cancers with mutated and



Paraffin blocks with tumour tissue from which the CeGat scientists isolate DNA for analysis using the somatic panels.

overactive EGFR. Other mutations make the tumour unresponsive to gefitinib. "Nowadays, quite a few highly-specific anti-cancer drugs are available," said Menzel.

High-throughput sequencing for analysing 551 genes

The detection of somatic mutations using CeGaT's somatic tumour panel requires a sample of the tumour (obtained from biopsies or surgery) in addition to a normal tissue sample (usually blood) from the particular patient. The DNA is isolated and potential cancer-causing genes are amplified and subsequently sequenced using high-throughput sequencing systems. The sequencing data are compared with those of a reference genome and potential sequence differences are further analysed. CeGaT's team of experienced scientists and medical doctors prepares a medical report, which is presented to the treating oncologists. In addition to the results obtained with the tumour panels, CeGaT's analyses also take into account results obtained in clinical studies that address similar issues. It takes about four weeks from sampling to final results.

An analysis involving CeGaT's somatic tumour panel with more than 500 genes costs less than 5,000 euros. Compared with a single-gene analysis, which costs between 1,500 and 2,000 euros per gene, CeGaT's service is relatively cheap. Despite the low price, diagnoses based on high-throughput sequencing analyses are not covered by German health insurance schemes. Germany is currently one of only a handful of countries where high-throughput sequencing services are not yet reimbursed by the health insurance companies and is falling behind by international standards. Health insurance companies pay out a great deal for anti-cancer drugs, and savings could clearly be made in cases that are unresponsive to therapy. This would also avoid stress and personal suffering for the patients involved. "I hope that billing codes will soon be introduced and that high-throughput sequencing services, and hence also somatic tumour panels, will be covered by the health insurance schemes. At the moment, there is a lot going on, and I am confident that we will not have to wait that long for

changes," concluded Dr. Menzel.

New methods under development

The demand for such investigations is understandably huge. CeGaT currently has a workforce of 62 people and continues to grow rapidly. The company plans to move into a new building in summer 2014, the construction of which began in April 2013. The company's tumour diagnostics department is already working on a new tumour diagnosis method which aims to analyse cell-free tumour DNA from patients' blood. A sensitive method of this kind would enable medical doctors to closely monitor healthy tumour patients and be ready to intervene in the event of tumour recurrence. Such a method is more sensitive than any CT examination, currently the method of choice for detecting abnormal growth.

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Cancer therapy and cancer diagnostics

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TRANSFERRING CODE TO DIAGNOSIS