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# Personalised Medicine

Excellence in  
Research –  
Responsibility  
for the Future.

# EDITORIAL

By using the most modern technologies available, we work to understand diseases in ways never before possible in order to offer our patients therapies tailored specifically to their needs. In this way, we combine the concept of personalised medicine with the hope of developing new therapies for previously untreatable and complex illnesses like cancer, dementia, cardiovascular diseases, and many others. These developments are possible only because of enormous advances in our understanding of the pathogenesis of diseases, because of our use of innovative technologies like genomic and proteomic analysis, and because of the introduction of new imaging techniques.

Prof. Dr. N. Malek

Personalised medicine is currently effecting fundamental changes in clinical therapy and therapeutic decision-making. Current clinic IT systems have barely been able to keep pace with changing needs. That's why a semantically homogenous revision of usable data is the greatest challenge to healthcare IT as it relates to personalised medicine today – and why it's the challenge we're focusing on here in Tübingen. The Quantitative Biology Center (QBiC) will help implement personalised medicine by applying its expertise in the areas of both omics-data analysis and the semantic integration of clinical and high-throughput data.

Prof. Dr. O. Kohlbacher



Chairman of the Center for Personalised Medicine (ZPM) and the platform 1 "Personalised Medicine" of the Excellence Initiative of the University Tübingen



Director of the QBiC (Quantitative Biology Center) and chair of the research department "Complex Diagnostics" of the ZPM

Personalised medicine is the result of a paradigm shift occurring today, leading us towards a causal, science-based view of medicine.

This view examines both the disease and the patient himself on a molecular basis in order to offer precise, individualized diagnoses. Multifactorial disorders, such as tumor formation, dementia, diabetes, and cardiovascular diseases, can thus be organized into specific sub-types (stratification), personalizing them so that they may be treated more efficiently.

Our goal is to prescribe the right medication for every patient in the right dosage at the right time by using precise, individualized medical care. This will lead to treatment which is both more effective and more efficient.

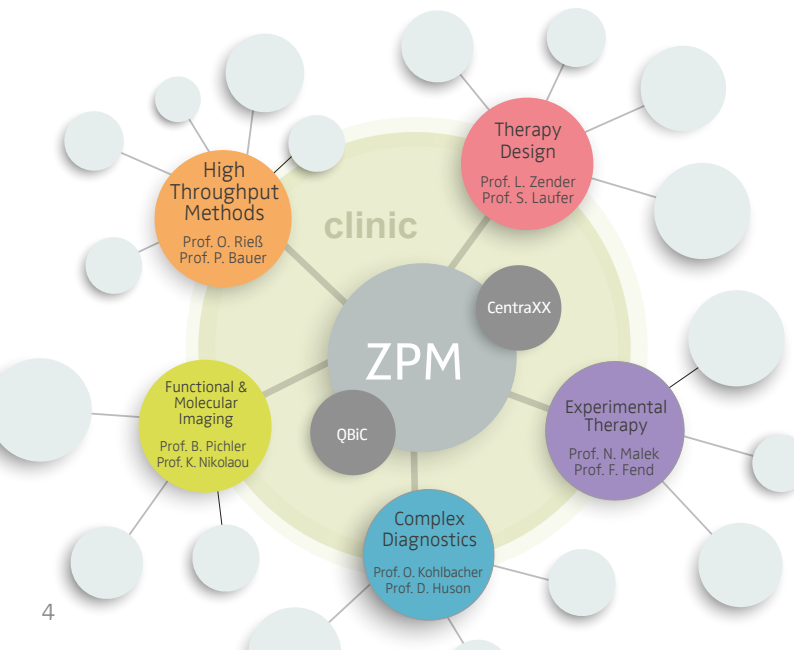


The complex technologies necessary for this process are only currently available at highly specialized institutions. The Center for Personalised Medicine (ZPM) was founded in close collaboration with the university hospital Tübingen (UKT) to accelerate introduction of these technologies into everyday clinical use, based on the platform 1 of the Future Concept line of the University of Tübingen's Excellence Initiative.

A total of 23 institutions from the fields of healthcare and medical research, engineering, and basic scientific research work together under one roof at the ZPM. They make personalised medicine (PM) a reality by addressing various key issues that form the framework for PM in a clinical setting.

These include the entire spectrum of high-throughput technologies (omics-technologies), the integration of functional and molecular imaging, and data analysis, as well as development and translational medicine with new therapies in our experimental clinic. The center's activities reflect the 5 priorities of the Excellence Initiative platform, linking these to the appropriate clinical areas.

Two representatives from medical or scientific research are responsible for each area. A central coordinating office works with both the center and the platform, keeping lines of communication direct.



One of the most important goals of the ZPM is to make all recorded patient data usable, from simple biosignals – like blood pressure or heart rate – all the way to highly complex omics-data from tumor tissue.

In order to complete our goals, we will:

build an integrated infrastructure that standardizes and links all relevant patient data to create individualized, multivariate disease profiles,

further develop high-throughput technologies and integrate them into clinical applications to achieve standardized, high-quality analytical data during routine hospital care,

develop systems medicine models for impartial interpretation of high-throughput data in order to prevent and predict the progression of individual diseases,

use knowledge gained to better understand diseases that did not previously respond to therapy,

promote the identification of new active compounds in order to develop innovative medicines and customized treatment strategies,

demonstrate the application of personalised medicine in clinical studies,

work towards structural and administrative strategies for applying personalised medicine in the UKT,

seek to build a dialogue with central figures in public healthcare to attract more focus to personalised medicine.

## From Data Analysis to Application

# BIG DATA

Because it collects such a wide range of expertise under one roof, the Tübingen Center for Personalised Medicine is able to meet the challenges of working with highly complex data sets and tasks.

The ZPM's IT infrastructure collects and integrates data from current clinic systems, making it available in a standardized user interface.

The clinical SAP system and the Quantitative Biology Center (QBiC) systems are linked, ensuring the smooth transfer of data. The QBiC not only provides the ZPM access to all available omics-technologies (i.e. genomics, proteomics, and metabolomics), but also offers bioinformatics solutions for data processing, analysis, and archiving.

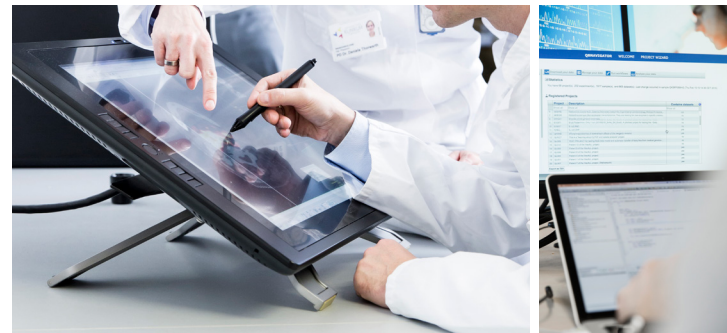


More data doesn't always mean more knowledge. Interpreting and evaluating data is often the greater challenge, requiring the skills of engineering-related disciplines like systems theory and IT expertise such as that used in systems medicine. Because the ZPM works closely with the university, we're able to use the synergies we discover within the Tübingen research community in the most effective way possible.

The ZPM's long-term goal is helping PM make the translational step out of the research lab and into the clinic.

We develop ideas for interpreting and visualizing data alongside cognitive scientists and IT professionals specializing in media in order to make data more useful for doctors on-site at clinics through user-friendly interfaces.

Another aspect of our work involves developing new, customized medications based on data gathered. We are planning to build an office on preclinical development in conjunction with the Pharmaceutical Institute at the University of Tübingen for this purpose. There, we will be able to evaluate promising target molecules, optimizing them in pre-clinical trials.



The office will also evaluate treatments which use approved medications in new indications to treat diseases with the same molecular characteristics, also called "drug repurposing." This not only reduces costs for development and approval, it also shortens the time medications take to reach patients.

Already completed translation can be found in “molecular tumor boards.”

Here, interdisciplinary teams of clinical oncologists, pathologists, radiologists, bioinformatics specialists, physician-geneticists and pharmacologists discuss tumor disease cases and develop treatment strategies based on clinical data like imaging, biopsies, and high-throughput data.

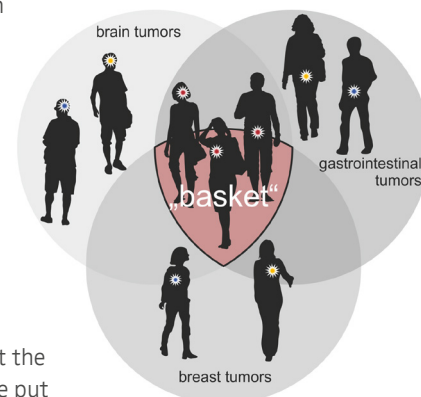
To establish this methodology for widespread use in the future, and to ensure a high level of quality, we develop guidelines for implementing these interdisciplinary boards and for collecting and analyzing information from cases previously treated separately.



The final step is applying our findings in clinical studies. We are able to do so quickly and in a highly targeted manner because of our already established Phase-1 clinical trials unit through the Comprehensive Cancer Center (CCC) in Tübingen, and because we work closely with the Center for Clinical Studies (ZKS). We are specifically focused on planning clinical studies according to the “n=1” principle, or so-called “basket trials.”

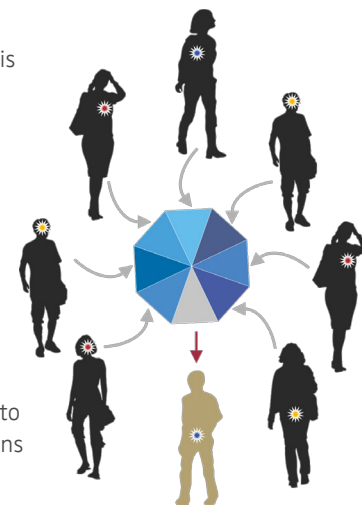
## Basket Trial

Clinical studies in which patients are treated based not on the type of tumor they have, but based on its molecular profile, fall into the category of “basket trials.” For example, breast, skin, and gastrointestinal tumors that have the same mutation, but not the same organic origin, are put into the same “basket,” and treated with the same mutation-specific medication. This is what’s called a knowledge-based or evidence-based treatment approach.



## N=1 Trial

Each patient and each illness is unique, on a molecular level. Based on this knowledge, we do not place patients in these studies into groups, assessing their average responses to therapy. Instead, each case is treated individually. The results of all these individual cases can then be correlated for use in predictive modeling, in order to make individualized predictions for future patients.





## Personalised Treatment is Already a Reality

# APPLICATION OF PM

The scientific groundwork for personalised medicine has been laid within the past 15 years. Positive examples from a wide spectrum of clinical indications prove that its translation into everyday clinical practice is not only medically feasible, it also makes good economic sense.

### Examples of personalised medications approved for use in Germany:

Ivacaftor: first causal treatment option for cystic fibrosis when a specific mutation is present

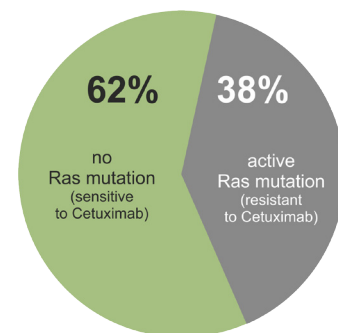
Ataluren: first medication to treat Duchenne muscular dystrophy; counteracts the genetic mutation

Lomitapid: treatment of very rare homozygous familial hypercholesterolemia based on the fundamental biological process

Cetuximab: approval for EGFR-expressing, metastasizing colorectal carcinoma without a Ras-mutation, i.e. the presence of the target molecule and absence of the resistance-conferring mutation

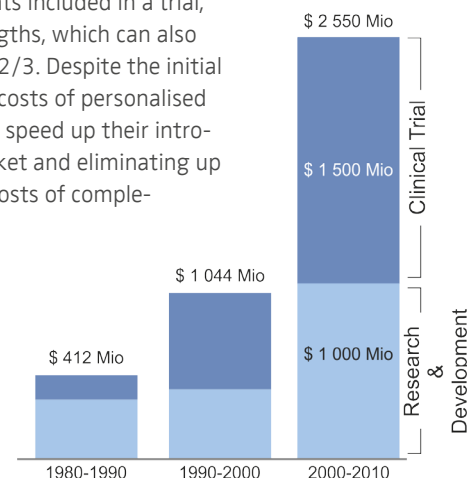
By explaining pathological mechanisms, we can treat or even heal previously non-treatable illnesses. We fight the causes of these illnesses, not the symptoms. Multifactorial causes are also often behind widespread diseases like cancer, diabetes, or cardiovascular diseases with superficially similar patterns of symptoms. Causal therapy is often impossible in these cases. However, precise stratification can greatly increase the likelihood a patient will respond to a therapy, helping predict side effects that are not taken into account in a classic, "one-size-fits-all" approach.

The economic and healthcare policy dimensions of personalised medicine are also worth mentioning here. Each time we eliminate a useless therapy, the patient gains time, is exposed to less danger of serious side effects, achieves an improved quality of life, and experiences lower treatment costs. A therapy using innovative antibodies like Cetuximab can easily cost 100,000 Euros per year, or more, but is not appropriate for over a third of patients who receive it, due to a Ras mutation.



Incidence of resistance-conferring Ras-mutation in colon cancer

More carefully characterizing patient collectives also hastens the development of new medications. Molecular stratification can drastically lower the number of patients included in a trial, shortening study lengths, which can also lower costs by up to 2/3. Despite the initial higher development costs of personalised medications, this can speed up their introduction into the market and eliminating up to 70% of the total costs of completing clinical studies.



Costs of drug development in the last 30 years

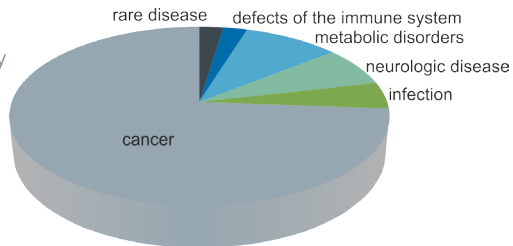


# PM – PRESENT AND FUTURE

The medical profession must rethink its approaches, especially in view of the demographic changes happening in almost all industrialized nations.

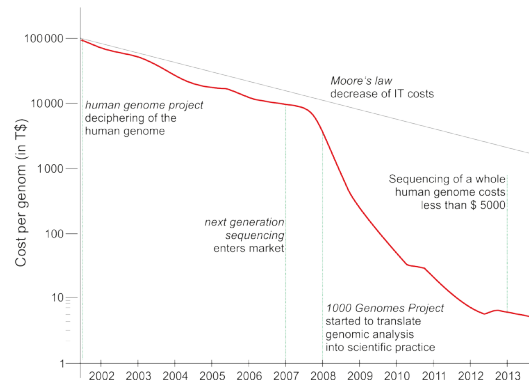
Increased demands on government related to medical research and systems medicine have led to a steady increase in PM. New, targeted medications are being introduced more and more frequently, especially for treating cancer. Nevertheless, in German hospitals, use of personalised medicine is still in the early stages. In Germany today, around 40 personalised medications have been approved.

Approved personalised medications in Germany in 2015 concerning their indication



Chronic diseases and age-related illnesses require increasingly long-term treatment. Customized, efficient treatment approaches with a low risk of side effects are becoming ever more important. These are economically feasible in the long term, and offer patients the best possible quality of life.

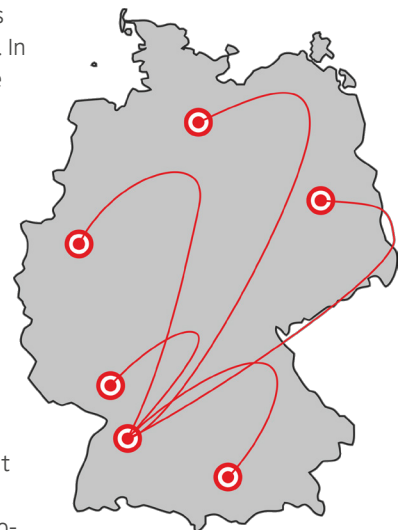
The molecular analyses needed for patient stratification are still fairly expensive today. Development in this area is, however, proceeding quickly. Just ten years ago, sequencing a human genome cost around 10 million USD, so expensive that routine clinical use would have been totally unimaginable. Today, the cost is around 5,000 USD and sinking, meaning use of this technology in everyday clinical treatment isn't just wishful thinking anymore.



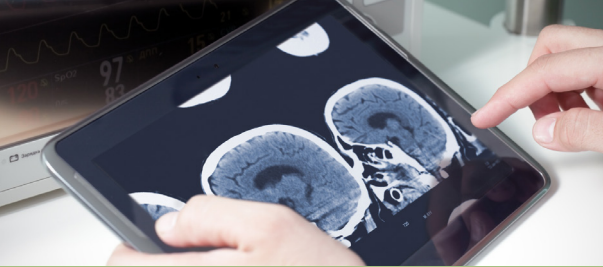
Since deciphering the human genome the costs steadily sank.

The key is collecting knowledge in order to apply it to clinical care. Besides the ZPM in Tübingen, there are also other centers focusing on the topic of personalised medicine. This leading-edge cluster of centers brings together resources and experts in each respective region

Established medical centers also play an important role. In Tübingen, these include the Comprehensive Infectious Disease Center (CIDiC), the German Center for Diabetes Research (DZD), and the Comprehensive Cancer Center (CCC), among others.



These serve as an example of how diverse institutions can successfully cooperate to achieve improved patient care. We believe pursuing a comparable model for personalised medicine is a worthwhile goal.



# IMPRINT

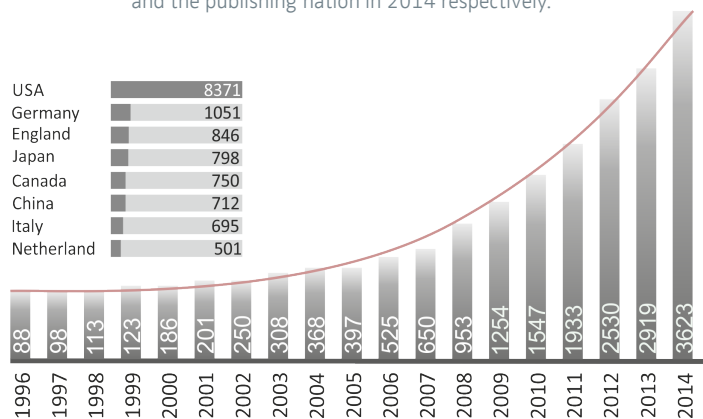
Germany needs to make considerable efforts to ensure it doesn't lose out in international competition.

In comparison to other European countries, Germany has taken on a pioneering role in researching personalised medicine. However, compared to the scientific output of the USA, it becomes clear that Europe, including Germany, is currently lagging behind.

In order to close the gap that already exists between Europe and the US, we need to not only combine forces, but also seek financial support from federal and state governments. Industries and health insurance companies must demonstrate their willingness to invest in personalised medicine and help carry the load together.

The Center for Personalised Medicine at the University of Tübingen is ready to promote a big idea: medical science that is both patient-oriented and fundamentally evidence-based.

Scientific publications on the topic „personalized medicine“ between 1996 and 2014 worldwide and the publishing nation in 2014 respectively.



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