BACKGROUND MEDIA INFORMATION

EARLY DETECTION
AND PERSONALISED MEDICINE

What Biomarkers Tell Us

Who is sick, who will get sick? Which patient should be treated with what and when? How well does the patient respond to treatment? And when has the patient returned to health? – For countless diseases today, biomarkers are providing physicians with valuable information. What are biomarkers? How will they help us in the future?

The right medicine at the right dose at the right time, rapid and inexpensive diagnosis, individualised prognoses and unerring guidance of treatment: it is a long-cherished dream of the medical profession to be able to individually tailor diagnosis and treatment for every patient.

This dream of personalised medicine could come true with the help of biomarkers. These could make it possible for physicians to be able to make predictions about the effectiveness of a treatment before it even begins. Individuals, for whom certain medications or treatments would be less effective, ineffective, or even damaging, could be treated with something else from the outset. Therapies could be precisely tailored for each patient, and the difficult balance between desired and damaging effects could also be found more quickly and accurately.

Biomarkers are not a discovery of the last twenty years. Even ancient Arabic, Hindu, and Chinese reports describe the sweet taste of the urine of patients whose symptoms, from today's point of view, clearly indicate diabetes.

In more modern medicine, it was the English physician Thomas Willis (1621-1675) who first described the connection between diabetes and sweet urine. Willis had observed that some of the numerous urine samples he collected from his patients and saved at home were clearly preferred by houseflies.[1] He logically concluded from this observation that these samples had a significantly elevated sugar concentration and then used a taste test to distinguish the "sweet" from the "tasteless" urine.

Biomarkers as the basis for personalised medicine

"Biomarkers are characteristic biological features that can be objectively measured and indicate either normal or diseased processes in the body." [2] This is the definition used by the Biomarkers Consortium, a coalition of many governmental institutions, organisations, and stakeholders whose aim is to advance established biomarkers and develop new ones.

► **What are biomarkers?**

Biomarkers are characteristic biological properties that can be detected and measured in parts of the body like the blood or tissue. They may indicate either normal or diseased processes in the body. Biomarkers can be specific molecules, or genes, gene products, enzymes, or hormones. Complex organ functions can also serve as biomarkers. Biomarkers are also very important in the development of new drugs.

For example, body temperature is a well-known biomarker for fever. Blood pressure is used to determine the risk of stroke. It is also widely known that cholesterol values are a biomarker and risk indicator for coronary and vascular disease, and that C-reactive protein (CRP) is a marker for inflammation.

Biomarkers can be cells, specific molecules, genes or gene products, enzymes, or hormones. In addition, biomarkers can be complex organ functions or general characteristic changes in biological structures.

It is necessary to distinguish between disease-related and drug-related biomarkers. **Disease-related** biomarkers give an indication of whether there is a threat of disease (risk indicator or predictive biomarkers), if a disease already exists (diagnostic biomarker), or how such a disease may develop in an individual case (prognostic biomarker). In contrast, **drug-related** biomarkers indicate whether a drug will be effective in a specific patient and how the patient's body will process it.

In addition to long-known parameters, such as those included and objectively measured in a blood count, there are numerous novel biomarkers used in the various medical specialties. Currently, intensive work is taking place on the discovery and development of in-

novative and more effective biomarkers. These “new biomarkers” have become the basis for preventive medicine, meaning medicine that recognises diseases or the risk of disease early, and takes specific countermeasures to prevent the development of disease. Biomarkers are also seen as the key to personalised medicine, treatments individually tailored to specific patients for highly efficient intervention in disease processes.
Often, such biomarkers indicate changes in metabolic processes. For example, if a patient has diabetes, the HbA_{1c} value for the “blood sugar memory” increases significantly (► see inset). In contrast, this value drops when a diabetic patient’s blood-sugar level is well controlled. The HbA_{1c} value thus serves as biomarker for monitoring treatment and gives information about the quality of blood-sugar control.[3]

The biochemical oracle

The “classic” biomarker is a laboratory parameter that the doctor can use to help make decisions in making a diagnosis and selecting a course of treatment. For example, the detection of certain autoantibodies in patient blood is a reliable biomarker for autoimmune disease.

The well-known rheumatoid factors are also nothing more than autoantibodies, antibodies formed by the immune system as a result of a misdirected immune response and targeted against the body itself. The detection of rheumatoid factors has been an important diagnostic marker for rheumatoid arthritis (RA) for over 50 years.[4 5]

► The HbA_{1c} value, “blood-sugar memory”:

The glycohaemoglobin value, also known as the HbA_{1c} value, is an important parameter for the control of blood sugar levels in Type-1 and especially Type-2 diabetics. It is aptly also referred to as the “blood sugar memory” of the patient.
Dependent on the blood-sugar concentration, a fraction of the glucose taken up by the red blood cells (erythrocytes) binds to the red blood component, haemoglobin. This forms glycohaemoglobin HbA_{1c}. In diabetics, the HbA_{1c} value can increase significantly and then reflects the average blood sugar level over the last weeks. If blood-sugar control is improved, the elevated values gradually come back down.

For the diagnosis of rheumatoid arthritis (RA), also known as chronic polyarthritis or “true articular rheumatism”, the antibodies against the bodies own citrullinated proteins are of particular value. These ACPAs, (ACPA stands for **A**nti-**c**itrullinated **p**rotein/peptide **a**ntibody) can be detected in the blood before the first symptoms of RA appear. They are thus valuable and highly predictive biomarkers for the early diagnosis of this autoimmune disease.[6] In addition, they indicate if the disease threatens to be severe with serious damage

to the bones and joints,[7] [8] which is an important tool for the doctor when providing a diagnosis and developing a treatment plan.

There are also more and more indications that ACPAs can be very useful in monitoring the success of treatment for RA. A French research group has reported that it is possible to directly measure the success of treatment by using the rheumatoid arthritis marker Anti-MCV.[9] This would make possible the accurate use of modern treatments with biologicals (► see inset). Physicians hope to soon be able to individually tailor rheumatoid arthritis treatments for each patient.

Biomarkers in targeted treatment

The concept of "personalised medicine" is increasingly becoming reality in the treatment of cancers. For example, the use of certain biomarkers makes it possible to estimate which cancer patients require additional chemo- or radiation therapy after tumour surgery, and which patients had best avoid this burdensome and stressful treatment, which may also increase the risk of subsequent tumour recurrence.

Biomarkers are particularly significant in targeted cancer therapy. This term refers to the treatment of patients with anti-tumour drugs that are directed very accurately against specific molecular features of the specific cancer in question.[10] The basis of this therapeutic concept is knowledge of the different signalling pathways and growth factors that drive the tumours in their uncontrolled cell division. In targeted therapy, particular agents and drugs are developed to very specifically intervene in these different signalling pathways, interrupt the malignant process, and thus slow or block tumour growth.[11] [12]

► Biologicals – biotechnologically produced drugs

Biologicals are substances produced with the latest biotechnology and at great technological expense, using highly complex development and preparation techniques.
Biologicals intervene precisely in the processes of the body. In cases of rheumatoid arthritis, for example, this type of "biological therapy" influences the immune system in such a way as to slow or even block the painful and destructive inflammation.

A prerequisite for this is detailed knowledge of the corresponding biomarkers, the molecular structures to which the cancer drugs can be applied. These could be the growth factors themselves, or receptor molecules on the mutated cancer cells. They could also be other, completely different structures at the molecular level, such as components of the cell membranes through which signals are transmitted into the cell.

What constitutes a good biomarker?

What are the demands that physicians, biochemists, and biotechnologists make of a good diagnostic biomarker? For chronic diseases, whose treatment may require patients to take medications for years, accurate diagnosis is particularly important – especially when strong side effects are expected from the treatment. In these cases, biomarkers are becoming more and more important, because they can confirm a difficult diagnosis or even make it possible in the first place.[13]

A number of diseases, such as Alzheimer's disease or rheumatoid arthritis, often begin with an early, symptom-free phase. In such symptom-free patients there may be more or less probability of actually developing symptoms. In these cases, biomarkers help to identify high-risk individuals reliably and in a timely manner so that they can either be treated before onset of the disease or as soon as possible thereafter.[14] [15]

In order to use a biomarker for diagnostics, the sample material must be as easy to obtain as possible. This may be a blood sample taken by a doctor, a urine or saliva sample, or a drop of blood like those diabetes patients extract from their own fingertips for regular blood-sugar monitoring.

For rapid initiation of treatment, the speed with which a result is obtained from the biomarker test is critical. A rapid test, which delivers a result after only a few minutes, is optimal. This makes it possible for the physician to discuss with the patient how to proceed and if necessary to start treatment immediately after the test.

Naturally, the detection method for the new biomarker must be accurate and as easy to carry out as possible. The results from different laboratories may not differ significantly from each other, and the new biomarker must naturally have proven its effectiveness for the diagnosis, prognosis, and risk assessment of the affected diseases in independent studies.

Biomarkers always deliver direct or indirect indications of the cause for the disease. With their help, the effectiveness of treatments can be evaluated and precisely measured, and new therapeutic concepts can be developed.

In the future, biomarkers will be particularly important in the area of disease prevention. Because they provide information about the risk of disease, make early diagnosis possi-

ble, and indicate disease long before onset, they will make certain diseases easier to control in the future.

Rheumatic diseases, cancer, and diabetes, as well as strokes and dementia-inducing diseases such as Alzheimer's: for many diseases and in many medical disciplines, biomarker research is being greatly advanced.[16] [17]The way in which biomarkers have thus far expanded beyond their role as a purely diagnostic tool indicates that they will continue to grow in significance in modern medicine. In the coming years, they could change and shape our understanding of treatments for numerous diseases and assume a central role in pharmaceutical and medical research.

For Editors:

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Do you need more information about biomarkers? – Please contact us:

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