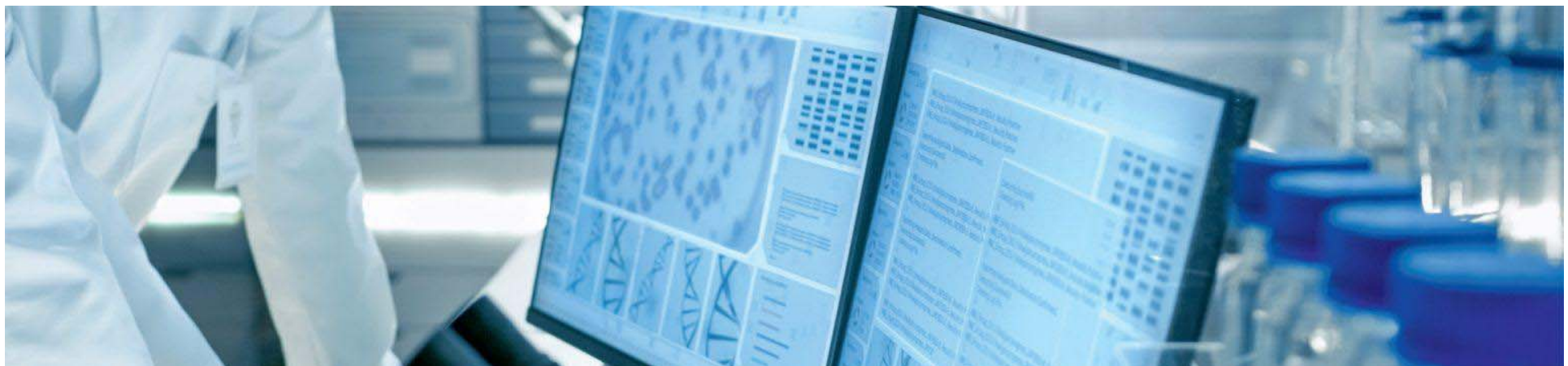




Prevention is better than a cure





Philipp Wild is betting on bio-databases to predict diseases and their course of development

Professor Wild, one of your main areas of activity is the prevention of cardiovascular diseases. Since 2010/2011, they have accounted for approximately half of all deaths worldwide.

Cardiovascular diseases are in fact frequently multi-causal. In addition to risk factors such as high blood pressure, diabetes, and nicotine abuse, genetic predispositions, family and social influences and environmental factors also play a role – as do mental illnesses and personality. A single factor normally only has a very small influence, but several ones can lead to illness through accumulation.

Since the risk factors are known, targeted prevention is possible. Unfortunately, health insurance companies often do not offer comprehensive prevention as part of

What options do physicians have to convey the significance of preventative healthcare?

One example is measuring the elasticity of blood vessels. In a young person, vascular walls are flexible, like rubber, but in a person with atherosclerosis they are as hard as a metal pipe – and this influences blood pressure, even if the patient does not necessarily feel anything. By comparing one's arteries to those of a healthy person of the same age, we can become aware of the changes and thus convince the patient to prevent the development or the progression of the disease through

For the Framingham Heart Study, approximately 5,000 healthy participants between 30 and 60 years of age were selected. The first results from this study were published in the mid-1960s: "Smoking has a negative effect on the health of the heart and circulation". In 1971, the children of the initial participants were enrolled as the second generation. And meanwhile, the study is now examining the third generation.

The results of the Framingham Heart Study were confirmed by other studies and they were further extended: The risk of a fatal heart attack is doubled for smokers. There is an almost linear dose-

standard service.

Why is it important to start with prevention as early as possible?

In most cardiovascular diseases there is something called a subclinical phase. During this time the body is able to compensate for the illness to the extent that we don't notice any symptoms. The first symptoms, such as heart stutters, heart palpitations, dizziness, and shortness of breath do not emerge until after 30, 40 or even 60 years of age. Treatment often starts too late, and as a consequence a complete cure is then no longer possible. At this stage, the disease can only be contained.

An initial illness often entails secondary diseases, which are usually harder to treat. Early prevention can prevent this. It can be difficult, however, to create acceptance for individual prevention among younger people. Because they are healthy, they often don't see the need.

modifying their behaviour.

Beyond this, there are numerous medical studies whose results speak for a timely prevention of cardiovascular diseases. One of the most influential epidemiological studies in the world is the Framingham Heart Study. They began to systematically examine the population of the city Framingham in the USA in 1948 to explore the causes and risks of heart attacks and atherosclerosis.

Even then, cardiovascular diseases were among the most common causes of death in the USA. They were considered strokes of fate. When President Roosevelt died within two hours after suffering a cerebral haemorrhage on 12th April 1945, it was a complete surprise to his contemporaries. No one had any awareness that years of untreated hypertension had led to this event.

response relationship between the number of cigarettes smoked per day and the risk of developing a cardiovascular disease. Passive smoking increases the risk for these diseases by 21 percent.

So the results of the Framingham study have led to lasting changes for the better?

In Germany, the non-smoker protection law to protect passive smokers went into effect on 1st September 2006 – not until about 40 years after the first publication of the Framingham results. That's a long time to react to the finding that smoking in any form – active or passive – is bad.

A statistically proven success that has resulted from this legislative measure is that the prevalence of smoking, the percentage of people aged 15 or older consuming any form of tobacco, has decreased in Germany since the beginning of the 21st Century.



Development of percentage of smokers in population of Germany between 18 and 56 years of age over time



But medical research is already facing new challenges.

Currently, smoker prevalence is increasing again. E-cigarettes were developed by the industry as a safe alternative to conventional tobacco consumption. While the nicotine content is lower, with every puff a chemical mixture is inhaled whose effects in this combination have not yet been sufficiently examined, but which is harmful according to what we know so far. There are no findings from studies on the long-term effects yet. Medical science can therefore not yet assess the risk with ultimate certainty.

The obtained data volume is many times larger than that from routine examinations at a clinic. The bio-databases we are creating in Preventive Cardiology at the University Medical Center Mainz on population health and various diseases currently encompass about seven million biosamples of extremely diverse biomaterials.

What distinguishes systems medicine from conventional studies?

Conventional studies usually only refer to two levels in their analysis, for example, the entire genome and the presence or absence of disease. They are supplemented by individual tests

The utilisation of machine learning in this context means that if an explanatory pattern can be deciphered, physicians can intervene therapeutically in a preventive manner, or they can develop appropriate treatment approaches for already manifest disease.

These new options become more significant when you consider the fact that, for example, diseases already overcome by an individual can affect health development. People frequently become more multimorbid due to successes in medicine; they have a number of diseases and are prescribed various medicines simultaneously, which can interact with each other. This makes

The fast pace of current times poses increasing challenges to the medical sciences. One response to these challenges is the still relatively new area of “systems medicine” that relies on new, innovative IT technology and the use of large existing data volumes for new findings and research.

Do you see systems medicine as the future of preventive medicine?

Yes. Systems medicine will make it possible for us to provide effective and sustainable prevention. Digitalisation makes it possible. The central resources of current scientific work are interdisciplinary studies and the resulting biomaterial databases that deliver fast, reliable and comprehensive results.

In addition to previously determined health-relevant data, additional data will be gathered with a focus on family, social, and environmental aspects. This includes lifestyle, job history, personality traits, social and financial situation, living conditions, and also exposure to noise or fine dust. We want to improve the conditions in which the data on health status are collected by carrying out differentiated analyses under

depending on the specific issue in question. In systems medicine, we select several data levels: the genome, the activity of individual genes (epigenetics) and the regulation of molecules derived from this, for example proteins. The system-wide approach is thus also able to explain *why* illnesses occur. Genetic predisposition alone does not usually lead to illness, but rather it is the combination of genetics with additional risk factors that does, although these additional risk factors may also partially be genetic in nature.

To analyse such large data volumes and gain insights, you have to travel new paths. What is the role played by “artificial intelligence”?

It undoubtedly plays a central role. We are very active in the area of machine learning, but also that of deep learning, which is based on how the brain functions. These both represent subfields of artificial intelligence.

The result is determined on the basis of knowledge that has already been acquired. Software makes it possible to test all variants with combinations of data points that are connected to the

can interact with each other. This makes treatment increasingly complex.

Please give us an example.

If contracted while a child or teenager, the chances of surviving cancer is 84 percent. A study at the University Medical Center Mainz showed: the treatment of this disease, the traumatic experience, its effects on future lifestyle and also on epigenetics can lead to risk factors for other diseases in that individual: psychological illnesses, reduced fertility, and the risk of contracting a cancerous disease a second time. Analyses have also shown that even in younger years there is a higher probability of contracting a cardiovascular disease as sequelae.

Systems medicine makes it possible to identify certain structures and patterns of disease development – in this case through interdisciplinary studies in cardiology, psychology and psychosomatics, and cancer medicine.

Many disciplines are involved in the collection, processing, analysis and interpretation of all parameters: doctors, bioinformaticians, IT specialists, biostatisticians, health scientists,

standardized conditions, for example, the same time of day, sitting position and constant external conditions for the test. Through high standardization, for example in measuring blood pressure, EKGs, or the taking of blood samples, random mistakes are reduced, making the measurement of data more reliable.

occurrence of a disease. With the help of billions of computational processes and the scientific evaluation of the calculated signatures, the prognosis for the occurrence or non-occurrence of a disease can be deduced.

biologists, biochemists, toxicologists, data managers, documentalists, medical-technical employees, medical assistants, study nurses, and study assistants responsible for carrying out the study according to the study plan.

From the risk catalogue for cardiovascular diseases

| Risk factors for cardiovascular diseases | Recommendation |
|--|---|
| Blood pressure | < 140/90 mm Hg |
| Diabetes mellitus Type 2 | <ul style="list-style-type: none"> • Diet: no rapid sugars (dextrose, sucrose in sweets) • regular exercise • no smoking • Avoid irregular night-day rhythm |
| Body weight | BMI = Body-Mass-Index : $\frac{\text{weight (kg)}}{\text{height(m}^2\text{)}}$ 60 years+, ideal about 27 kg/m ² |
| Abdominal girth | Women < 80 cm Men < 94 cm |
| Ratio abdominal girth/ height | no recognized threshold value |
| Blood fats: • LDL-Cholesteol "bad cholesterol" • Triglycerides (neutral fats, main component of dietary fat) | Threshold value for people • with no cardiovascular disease 160 mg/dl • depending on risk (130, 115, 100, 70 mg/dl) lifestyle changes: diet, regular exercise |
| Smoking: passive/active smoking Substances: nicotine, tar E-cigarettes in addition: | no smoking |



Professor Philipp Wild is Professor for "Clinical Epidemiology and Systems Medicine" at the University of Mainz. He also heads the "Clinical Epidemiology" at the Center for Thrombosis and Hemostasis and "Preventive Cardiology and Medical Prevention" at the Center for Cardiology. He has been Principal Investigator in the

| | |
|---|---|
| vapor substances, aromas, liquids | |
| <ul style="list-style-type: none"> possibly harmful substances Vaporizing produces poisonous substances | |
| Adiposity (obesity) lack of exercise | BMI-threshold > 30 kg/m ² : lifestyle changes: diet, physical activity |
| Psycho-social factors | |
| Genetic factors | |
| Environmental factors | |

German Centre for Cardiovascular Research (DZHK) since 2012, and since 2013 Speaker of the DZHK for the University Medical Center of the University Mainz. In 2015 he was also named Speaker of their Research Centre for Translational Vascular Biology.

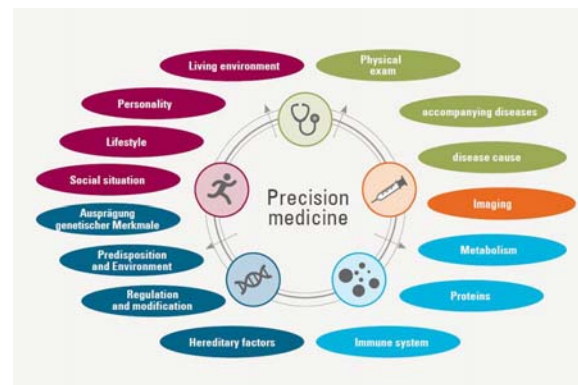
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The consequence of this research is that in the future we will recommend a follow-up examination programme for at-risk patients that does not just focus on cancer, but also on cardiovascular diseases and psychological diseases.

Systems medicine can provide the knowledge necessary for personalized medicine, treatment that is custom made for that person. The patient can be advised much better and more sustainably based on his or her existing biodata and lifestyle, both preventatively and when treating already manifest disease.

Against this background, it was determined during the Gutenberg Health Study (GHS) by the University

The next step is determining which mechanisms of chronic venous insufficiency besides inflammation are responsible. Studies incorporating this aspect will continue and therapeutic targets will be developed from those findings.



This diagramme illustrates personalized medicine, treatment that is custom made for that person

Based on your research so far, how do you see medicine developing in the future?

Systems medicine enables us to decode mechanisms of complex, multicausal diseases, to identify risk factors, and to identify starting points for the development of new medications. A specific and efficient diagnosis makes early detection and, consequently, treatment of diseases possible.

Treatment itself becomes more effective and simultaneously less invasive through the development of new medications, and through the avoidance of unnecessary medication and the resulting side effects. In cancer treatment, for example,

Medical Center Mainz that the risk catalogue for cardiovascular diseases and the risk factors for chronic venous insufficiency need to be expanded. How do you assess the medical significance?

Chronic venous insufficiency was previously considered a cosmetic problem caused by a microcirculatory disturbance in connection with changes in the venal wall of leg veins. Its symptoms are swollen, tired, heavy legs with spider or varicose veins. Its most frequent cause is a vein weakness, or sometimes also a leg vein thrombosis. Due to an increase in the inflammation level in the body, this disease also contributes to the development of atherosclerosis, independently of previously known risk factors. This was not known previously.

A systems medicine examination reveals a raised inflammation level in the body. The inflammations occur locally in this disease and are therefore limited to one area, but, interestingly, they lead to the measurement of slightly higher values throughout the body as well as a systemic change. It is known that

In view of the large amount of data, are you taking special measures with regard to data security?

Absolutely. A lot of data means a lot of knowledge. Knowledge is power, and this can be abused if it falls in the wrong hands. Data security has to be transparent and secure. Otherwise, people will not continue to be willing to provide their data for research purposes. That would deprive systems medicine of the foundation of its scientific research.

Extensive data security measures include data anonymization and restricted data access, i.e., each specialist group stores its data individually. In addition, each staff member or researcher only has access to data that is relevant for his or her field of work. Every two years, the collection, storage and handling of data is evaluated by the ethics committee and local data security offices.

chemotherapeutics stop the growth of cancer cells, but also the growth of healthy tissues such as hair root cells and mucous membranes in the mouth, intestines and bladder. The targeted use of new tumour-specific chemotherapeutics offer improved probabilities for cures with an improved quality of life.

Regarding precision medicine, systems medicine is a crucial component for developing a holistic concept of individualized healthcare for each person. It is often still too expensive, but it is the future. We must, however, continually ask the question: How much prevention is beneficial for a person? Every individual has a right to know or not to know his or her health status, but also the right to act or not to act.

Regina Kremer conducted the interview

inflammation, even when caused by allergies or periodontitis, promotes the development of atherosclerosis and cardiovascular diseases.

This article originally appeared in German in the research magazine Forschung Frankfurt 2/2019 “von Herzen”

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