Genetic testing for the prevention of diseases?

Genetic testing is beginning to play an important role in personalised medicine and is indispensable for the diagnosis and therapy of many diseases. However, the preventive and diagnostic power of many genetic tests is still inferior to traditional diagnostic tests. In addition, commercial genetic tests do not always live up to the claims made about them.

The sequencing of the human genome, which was heavily publicised around the world ten years ago, was celebrated by scientists and politicians alike as the beginning of a new era of medicine and health care. It was envisaged that the sequencing of the human genome would enable doctors in the future to determine any individual's genetic predisposition to certain diseases, identify risk factors and find strategies to prevent the development of disease, or treat it, if the disease could not be prevented. Such developments would bring us towards personalised medicine, tailored to the individual requirements of a patient. The determination of an individual's genetic composition on the basis of the sequenced human genome seemed to create the conditions required for such treatment to be possible.

The MTHFR gene test

Ever since DNA sequencing and hybridisation methods became routine applications, many laboratory physicians and human genetics laboratories have offered predictive gene tests to assess
a person’s susceptibility to disease. The example of the emerging field of nutrigenetics, a science that is focused on matching a person’s nutritional requirements to their genes, will be used to reveal the pro's and con's of such gene tests: The new techniques can be used to identify people who possess a defective, only weakly active form of the enzyme methylenetetrahydrofolate reductase (MTHFR). The MTHFR tests are used to test individuals for mutations in the MTHFR gene in order to identify a genetic aetiology for hyperhomocysteinemia. When eating normally, these people have an elevated homocysteine level, an amino acid that is suspected of increasing a person’s risk of myocardial infarction and stroke. The homocysteine level can be decreased by consuming foods rich in folic acid (vitamin B9, which is for example found in fresh vegetables and fruit). This seems like a convincing argument for a person to undergo genetic testing in order to prevent cardiovascular diseases at the same time as being excellent news for the providers of MTHFR tests and the manufacturers of vitamin preparations.

**Folic acid:**
The US Food and Drug Administration now requires the addition of folic acid (folate) to enrich flour and cereals. Although there is substantial evidence that the uptake of higher folic acid levels reduces the risk of colon cancer and potentially also other types of cancer, legal regulations requiring the addition of folic acid to basic foodstuffs are still a matter of controversy in Europe due to evidence suggesting that folate is also able to promote the growth of early-stage tumours. However, agreement exists on the consumption of supplemental folic acid in addition to a healthy diet prior to and during pregnancy. It has been shown that folate-rich foods or folate supplements reduce neural tube defects in unborn children (see "Cornelia Ulrich: Cancer prevention through food and sport").

Arteriosclerotic plaque in a coronary vessel  
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MTHFR gene tests to prevent cardiovascular diseases are now heavily contested. As discussed in the renowned Journal of the American Medical Association (for example JAMA 299, 2086-2087, 2008), some large-scale studies have shown a positive relation of diet and disease prevention, while others found that elevated vitamin B9 intake does not lead to a reduction in myocardial infarction and stroke risk. Other B vitamins (vitamin B6 and B12) have also been shown to play a role in the development/prevention of cardiovascular diseases. The relationship between homocysteine level and cardiovascular diseases seems far more complicated than initially thought. Basically, the example confirms what has been known for a long time: Cardiovascular diseases (as well as many other common diseases such as diabetes and cancer) are the result of a broad range of factors and of the interaction of many genes.

The PROCAM study
The International Task Force for Prevention of Coronary Heart Disease, in which leading European arteriosclerosis researchers work together, has established a multifactorial diagnostic approach to assess an individual’s risk of myocardial infarction. The approach is based on the largest study worldwide (PROCAM – Prospective Cardiovascular Münster Heart Study) on the determination of myocardial infarction risk factors which has involved around 40,000 people since 1979. Prof. Dr. Gerd Assmann and his colleagues have used the comprehensive dataset to develop a mathematical method that enables the assessment of risk factors with high probability. Assmann is the executive director of the Task Force and head of the Institute of Arteriosclerosis Research at the University of Münster.

The “PROCAM Health Check” includes laboratory test results such as the LDL cholesterol blood level (generally known as ‘bad’ cholesterol), HDL cholesterol (‘good’ cholesterol), triglycerides and blood glucose levels, but also blood pressure, age, familiar predisposition and smoking. By entering patient data into the interactive website of the "International Task Force for Prevention of Coronary Heart Disease", physicians can obtain immediate results and call on their patients to change their lifestyle if necessary. The study suggests that such checks should be carried out before taking lipid-reducing drugs (statins). A PROCAM Quick Test, which does not require the entry of laboratory test results, is available from the same site to anybody who wants to find out his or her coronary risk.

The danger of misuse

Even though the previous paragraph focused on showing that the rather unsophisticated conventional acquisition of data is superior to genetic tests in its ability to predict coronary risk, this does not mean that the benefit of genetic tests needs to be questioned. Genetic testing has become an integral part of diagnosis in the field of oncology, which is the field where personalised medicine has made the greatest progress. Prior to the treatment of breast cancer patients with trastuzumab (Herceptin®) or chronic myeloid leukaemia patients with imatinib (Glivec®), the patients are legally required to undergo genetic testing to determine drug dosage and predict the treatment outcome. This essentially means that these genetic tests are used to determine the responsiveness of the patients to treatment, rather than to determine disease risk and prevent the development of disease.

Shortly after the magic moment in science on 26th June 2000, when Francis Collins and Craig Venter, together with President Bill Clinton, announced that the human genome had been deciphered, many companies were established in the USA offering direct-to-consumer gene-testing kits for the diagnosis of genetic diseases and prediction of disease risk. Some of these tests are misleading and of no practical use, and their marketing borders on the fraudulent and deceptive. In Germany, the situation is fortunately regulated by the Gene Diagnostics Law which requires doctors to be involved in such diagnoses. However, the expanding Internet trade, which is difficult to regulate, enables people to order direct-to-consumer (DTC) gene-testing kits online from abroad - and the number of people making use of this opportunity is growing. It is only possible to prevent the misuse of genetic testing when the genetic testing laboratories are inspected by public authorities and the tests examined by independent experts. Only then will the genetic tests fulfil the hopes attached to personalised medicine.

The USA and Great Britain appear to be moving away from the current laissez-faire attitude. In a public hearing on the regulation of gene tests in 2010 organised by the American Food and Drug Administration, the FDA concluded that commercial genetic tests should be regulated as medical
devices and be federally approved as safe and effective. On 4th August 2010, the Human Genetics Commission commissioned by the British government issued a ‘Common Framework of Principles’ for direct-to-consumer genetic testing services in which it calls for genetic testing to be carried out only in certified laboratories that work in conformance with controlled quality standards. In addition, it also requires test providers to support claims about the clinical validity of tests offered by relevant evidence published in peer-reviewed scientific literature.