Algorithm Determines the Appropriate Drug

The goal of Professor Mikko Niemi is to devise an interpretation algorithm that helps doctors determine the appropriate drug and correct dosage for a patient. Treatments become more effective and side effects are reduced, thereby decreasing the costs.

People react differently to medications; the efficacy of drug treatment remains insufficient for some, while others suffer from adverse effects. The reason for the atypical responses may be our physical characteristics, other medication and each person's genetic makeup. An algorithm could be used to help predict the necessary dose or adverse effects of a drug when data on the patient's genome is also available in addition to physiological information from the patient. A genetic test can be performed through a simple blood sample.

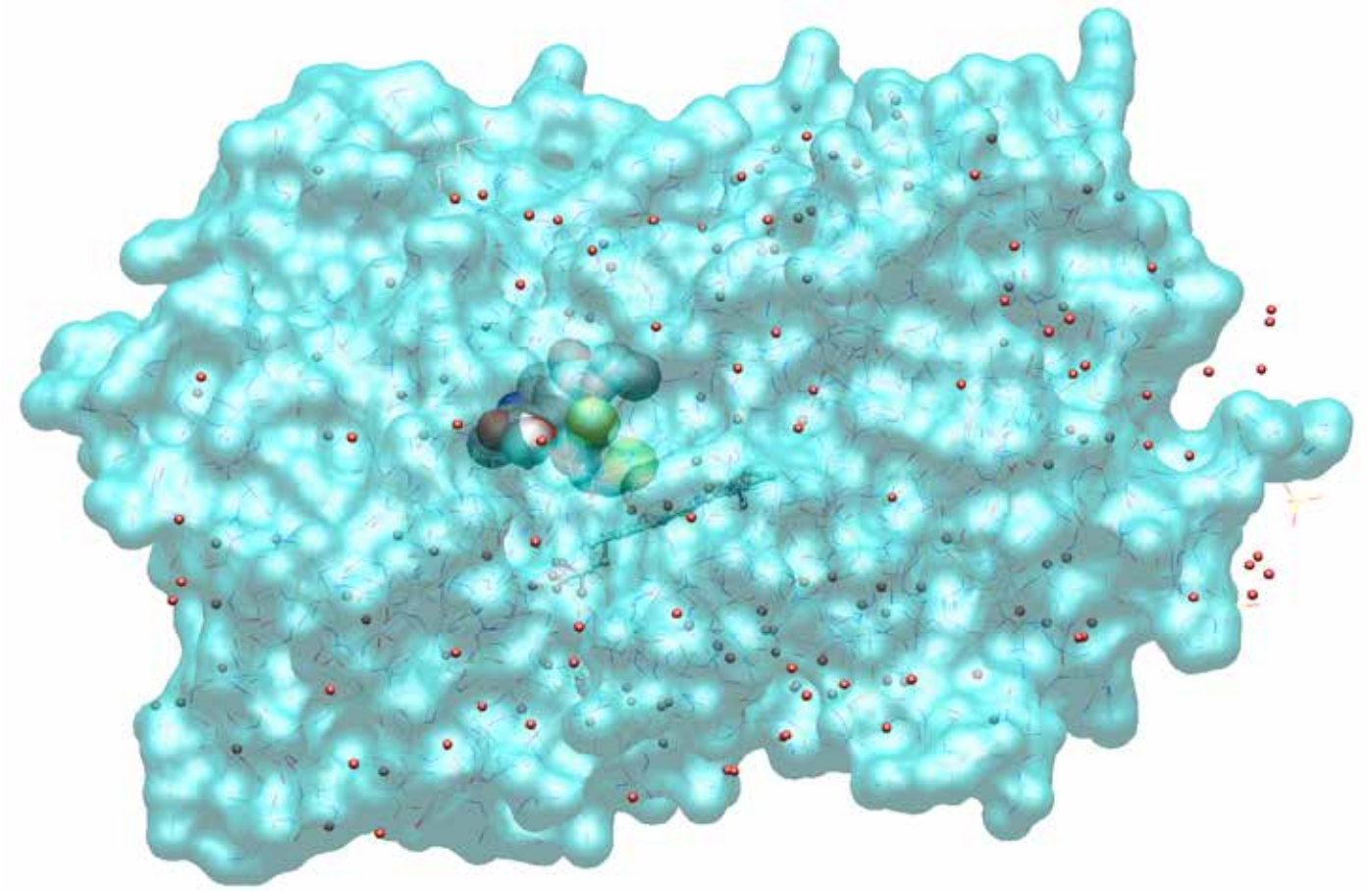
New information about the human genome is obtained all the time. At the same time, the costs of genetic research and bioinformatics have fallen significantly. Data is accumulated and there are many new opportunities for utilising it. Pharmacogenetics is the study of the effect of genes on the efficacy and safety of drug ingredients. If the data on patient genomes was available to doctors, medication costs and significant adverse effects would often be reduced. The number of days in hospital care would also decrease.

"A genetic test can be performed through a simple blood sample."

"If the genomes of patients were tested systematically, drug treatments could be better tailored and their dosages measured more individually", says Professor of Pharmacogenetics and Chief Physician **Mikko Niemi**.

Niemi is leading a research group at the University of Helsinki studying how genes affect the concentrations, safety and efficacy of drug ingredients. He is also investigating when genetic tests should be considered in drug selection.

"The information on the results of the genetic test should be available when a medication is prescribed, but generally you have to wait a week or two for the



Cytochrome P450 (CYP) enzymes are some of the most important enzymes that break down drug ingredients. Pictured is the three-dimensional structure of the CYP2C8 enzyme.

result. It could, therefore, be sensible to proactively test for the most important genetic variants affecting drug treatments. Through our research, we seek to identify those patients who would benefit the most from such proactive testing."

Niemi's research group is also developing decision-making support systems related to pharmacogenetics. The aim is to devise an interpretation algorithm for doctors treating patients with cardiovascular disease to help find the most effective and safe cholesterol medication for each patient. The algorithm uses data on the patient's characteristics, illnesses, other medications and genome.

Statin drugs intended for cardiovascular disease reduce the level of LDL cholesterol and increase the level of good HDL cholesterol in the blood. However, they cause muscle pain in some patients. The predisposition for muscle symptoms is partly hereditary.

"The algorithm uses data on the patient's characteristics, illnesses, other medications and genome."

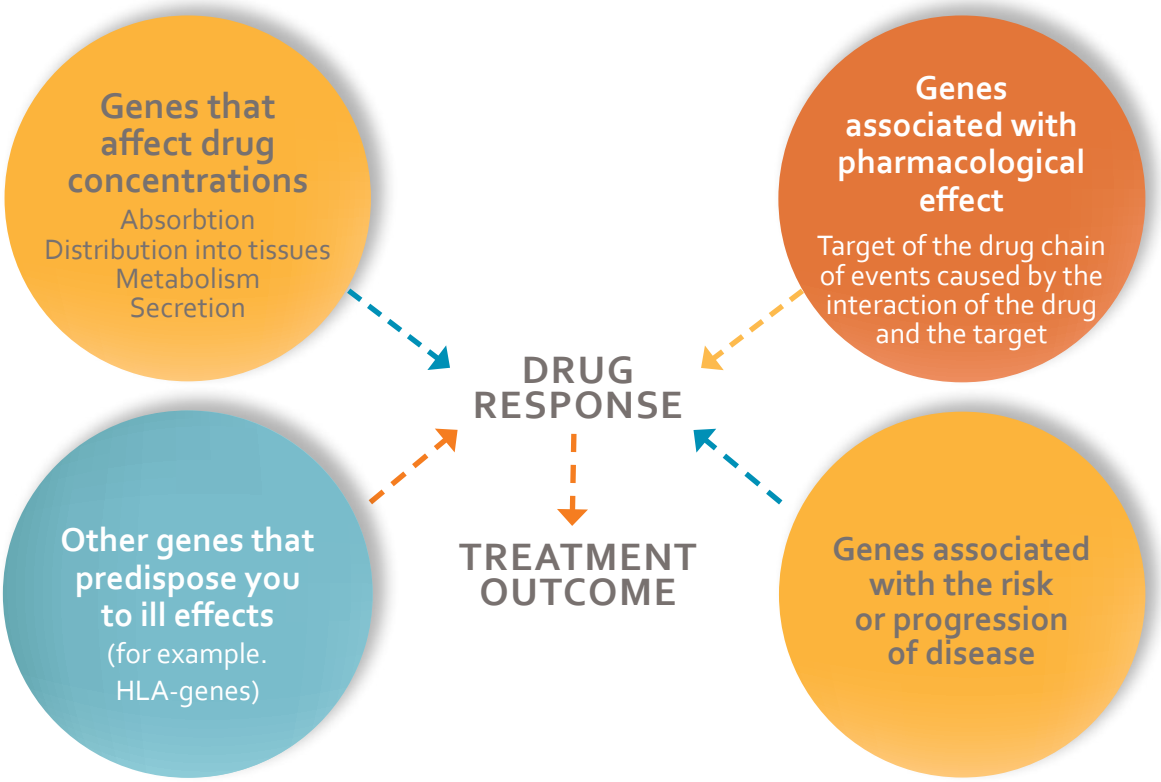
Drug metabolism is individual

The dosage requirement of individual drug ingredients may vary by more than tenfold between different individuals. This may result from how rapidly or slowly the drug leaves the body. Cytochrome enzymes (CYP) are central to the breakdown and removal from the body of many foreign substances, such as drugs. CYP enzymes are present especially in the liver.

When Mikko Niemi was working on his doctoral dissertation on the synergistic effects of diabetes drugs, he suspected that the variation in drug metabolism in different individuals was hereditary. Of particular interest are the three CYP enzymes CYP2D6, CYP2C9 and CYP2C19, as they affect up to one third of all drug ingredients in clinical use. Genetic variation in the activity of the CYP enzymes is high. This variation may lead to manifold differences in the concentrations of different drug ingredients and the responses to them in different individuals.

Genetic tests allow people to be classified into up to four different groups, depending on the drug, based on how quickly the body eliminates certain drug ingredients: very fast, normal, slowed down and slow. This so-called metabolic rate can affect the dosage requirement, efficacy and adverse effect risk of a drug.

In very fast metabolisers, the drug ingredient leaves the body faster than normal and its effect can be insufficient. In slow metabolisers, the drug exits slower than normal and its effects may be intensified. Consequently, the same drug dose may be too low for some and too high for others.



Genes that affect drug treatments.

"Genetic tests allow people to be classified into up to four different groups, depending on the drug, based on how quickly the body eliminates certain drug ingredients."

Some drugs become active by means of CYP enzymes. With such drugs, the effect of the hereditary metabolic rate is reversed. For example, in one third of the population, the effect of clopidogrel, a drug that inhibits blood coagulation, is weaker than normal due to hereditarily slowed down CYP2C19 metabolism. It is, therefore, advisable to opt for alternative medication with such patients.

Variation in the CYP2D6 enzyme, in turn, has a significant effect on, for example, codeine. Codeine is a common prescription painkiller, part of which usually turns into morphine in the liver via the CYP2D6 enzyme. In slow metabolisers, the effect of codeine may be inadequate. In very fast metabolisers, the amount of morphine in the body may run too high.

"Were the doctor to already know at the start of treatment that the patient's CYP2D6 metabolism is slow, the patient would not need to suffer from inadequate pain management."

Other enzymes besides CYPs are also relevant. TPMT, for example, is an enzyme that affects the metabolism of thiopurine drugs. Thiopurines are used to treat, for instance, autoimmune diseases, inflammatory bowel diseases and leukaemia.

"A hereditary TPMT deficiency predisposes you to the severe adverse effects of thiopurine drugs on blood cells. A genetic test to identify this hereditary deficiency has been in clinical use in Finland already since 2005", says Mikko Niemi.

Around a dozen genetic tests related to drug treatments are currently available in Finland.

Decision-making support algorithm for doctors

The suitability of a drug ingredient for each individual depends on many factors. It is not solely affected by enzymes that break down drugs. The transport proteins of the cell membrane affect the delivery of drug ingredients to their site of action. In the target tissue, the drug ingredient interacts with its target of effect.

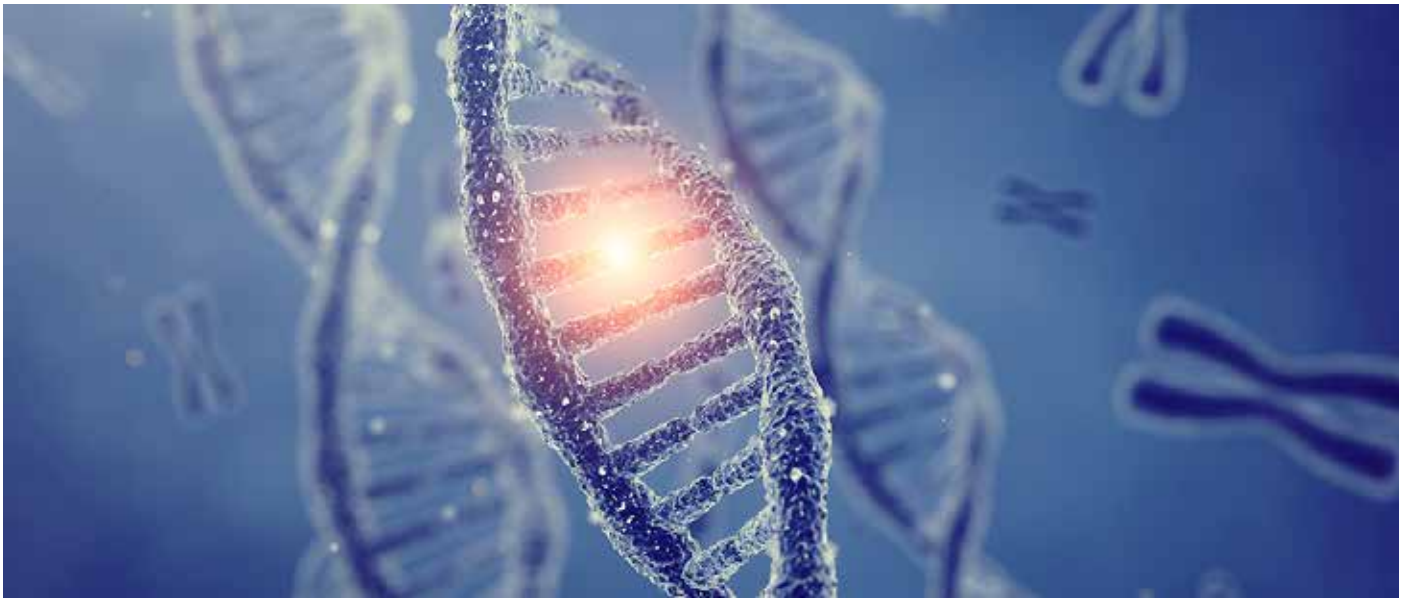
"This results in a chain of events that brings about the desired drug effect. There are individual, partly hereditary differences in all these factors. It would be important to consider all these individual factors, including the genome, when selecting medication."

In 2017, Mikko Niemi was granted substantial funding by the European Research Council for a project to develop an algorithm facilitating the selection of cholesterol medication. For this purpose, Niemi's research group is building a so-called system pharmacological model.

"It is a kind of virtual patient that can be used to individually predict the effects of each alternative cholesterol drug."

No similar algorithm has been attempted to date.

"If the algorithm works in the selection of cholesterol medication, a similar way of thinking could also be extended to other drug treatments."



Of course, the algorithm cannot be built if there is not enough reliable research data available. Niemi's research group has been compiling such data for years in their research projects. The biobanks established in Finland and the future genome centre will also speed up the collection of data needed for such research.

Better utilisation of genetic information is also desired by the Finnish state. Due to Finland's exceptional settlement history, the genetic structure of the population provides special opportunities to combine genomic and health data. Pharmacogenetics is one of the four leading projects of the national genome strategy. The goal of the strategy is to have genetic data in efficient, health-promoting use already in 2020.

Pilot project: utilisation of genomic data in health care

At present, the number of genes with significant effects on the efficacy and safety of drug treatment is relatively low: less than 20 of the total of about 20,000 human genes.

Since the group of genes is so small, according to Mikko Niemi, it would be technically possible to test even large numbers of patients.

"The next step is to proactively test for all genetic variants affecting drug treatment."

The National Institute for Health and Welfare (THL), HUSLAB's Department of Clinical Pharmacology and CSC have launched a pilot project that will be implemented by combining the genetic data of THL Biobank and the patient document information of HUS. The materials will be used to map the prevalence of the genetic variants affecting drug treatments in Finns. In addition, the project will look at how many patients in the sample receive drug treatment during or after the treatment period wherein genetic data could have affected the selection or dosage.

For the study, HUS and THL will have their own private and secure network connections to CSC's data centre. This will allow HUS and THL to process data quickly and efficiently.

Sufficient long-term storage and data transfer at a speed of at least 10 Gbit/s to the systems of HUS and THL are prepared for in the project, and the necessary number of virtual servers for processing information is provided for the pharmacogenetics software environment.

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