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EU-funded researchers have developed a DNA test to help determine the correct dose of anticoagulant medication for people at risk of thrombosis, a blood-clotting condition that affects millions worldwide. Their work is advancing the emerging field of pharmacogenetics that aims to provide patients with personalised and more effective treatment based on their genetic profile.

Most thrombosis sufferers are treated with coumarins – oral anticoagulant drugs such as warfarin, acenocoumarol and phenprocoumon that work by reducing the clotting action of vitamin K in the blood. Millions of mostly elderly people depend on the anticoagulants to prevent potentially fatal clots, but getting the dose correct for each patient is difficult and risky: too much and the patient can suffer from internal bleeding, too little and the treatment will have no effect.

“Coumarins are in the top three drugs that cause hospital admissions,” notes Anke-Hilse Maitland-van der Zee, associate professor of pharmacogenetics/genomics at the University of Utrecht in the Netherlands. “It is therefore very important to predict in advance the dosage that a patient needs to keep them in the target therapeutic range for anticoagulation.”

With that goal in mind, researchers from across Europe came together in the EU-funded EU-PACT project to develop a predictive genetic test and algorithm to enable doctors to rapidly identify the right dose for individual patients. Their approach is based on evidence that genetic factors impact how patients respond to coumarins, particularly the presence of variations in two genes involved in vitamin K reduction. People with those polymorphisms (genetic variations), who are given a standard dose of warfarin – acenocoumarol or phenprocoumon – are most at risk of serious side effects. Today, frequent blood analysis during the early stages of treatment is important to get the dosage right.

**Dosing based on DNA**

By testing patients’ DNA for the presence of those polymorphisms – a process known as genotyping –
before beginning treatment and inputting the results into an advanced algorithm that also takes into account patients’ physiology, other illnesses and prescribed medications, the EU-PACT team aimed to prescribe the right dose from the very start of treatment, reducing the risk of side effects.

The researchers conducted two clinical trials involving more than 1 000 patients in six countries. Patients prescribed warfarin spent 7% more time in the correct therapeutic range within the first three months of treatment after being genotyped compared to standard practice. Those treated with phenprocoumon or acenocoumarol spent 5% more time in the correct therapeutic range in the first four weeks of treatment.

Based on those results, an implementation study has been launched in the United Kingdom and the team is continuing to refine its technique and algorithm, while cost-effectiveness analyses are ongoing in both the UK and Sweden.

“The effects of genotyping are less significant than we expected,” says Maitland-van der Zee, who led the scientific coordination of the project. “But if the technique is used specifically for people who display the genetic variations, the effects would likely be greatly increased.”

One of the challenges therefore is overcoming the current cost of performing DNA tests and the limited availability of patient genotype information, something that the EU-PACT coordinator predicts will change with time as the fields of pharmacogenetics and personalised care advance.

In that regard, Maitland-van der Zee notes that the EU-PACT researchers are now drawing on the knowledge and experience gained in the project to apply genotype-based algorithms to improving the treatment of other diseases, including breast cancer and asthma.

See also:
CORDIS [3]

Project:
A pharmacogenomic approach to coumarin anticoagulant therapy

Project Acronym:
EU-PACT

Project website:
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