DNAs of our lives

The role of pharmacogenomics in modern medicine

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Different people can react quite differently to the same medicine. For one person, the medicine might be extremely effective, improving or eradicating symptoms. For another, it might fail to work or require a dose adjustment. For yet another, it could cause severe side effects.

Many factors account for such differences, including age, gender, body mass index (BMI), ethnicity, other medicines, and co-existing medical conditions. But even if all the above factors are the same, patients may still react quite differently to the same medication. This is because of our DNA—the way a person responds to a drug is a complex trait that is influenced by many different genes.

More than 100 drugs now mention pharmacogenomic biomarkers on their FDA-approved drug label. Pharmacogenomics is the study of the inherited variations in genes that determine drug response. Often the variations affect a small region of DNA, as small as a single nucleotide, known as a single nucleotide polymorphism (SNP). Many genetic tests are based on genotyping to determine which SNPs the patient has. Alternatively, sequencing may be used—a more complex process which determines the exact sequence of the relevant part of the genome.

At least three SNPs have an important effect on how individuals respond to warfarin—an anticoagulant given to patients with an increased risk of developing blood clots. Two of these SNPs occur in the gene that contributes to the metabolism of warfarin, *CYP2C9*. The third SNP occurs in the target enzyme of warfarin, encoded by *VKORC1*. Carriers of these SNPs are more sensitive to warfarin and require lower doses.

The aim of warfarin therapy is to keep the patient's INR (International Normalized Ratio—a measure of blood coagulation) within a target range, usually between 2 and 3. If the INR is too low, the risk of blood clotting remains, but, if the INR is too high, there is a new risk of bleeding. Many factors influence what dose of warfarin a patient will need and are taken into account when calculating what the first dose should be. This is important because optimizing the starting dose of warfarin shortens the time it takes before the INR is safely within range.

It is now possible to include the patient's *CYP2C9* and *VKORC1* genotype to further optimize the warfarin starting dose. But currently, genetic testing for a drug response has yet to become an integrated part of routine clinical practice, and warfarin therapy is nearly always started without knowing the patient's genotype. This is partly because in many clinical scenarios, treatment has to be started quickly and there is no time to wait for the results of gene testing to come from a lab, which may take days to weeks.

However, this is changing. In a recent trial, genotype results were delivered within 60 minutes of a cheek swab being taken, by nurses performing the genetic test near the patient. Patients who were randomized to the group

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that received genotyping and were found to carry a particular variant of the *CYPC19* gene were given an alternative drug that worked better for them (1). And perhaps in the not so distant future, all patients will pre-emptively have their genomes sequenced so that the most effective drugs are given, and the drugs with an increased risk of adverse events avoided (2, 3).

Currently, there are genetic tests for about 2,500 diseases, and a growing number of tests for variations in genes involved in drug responses. The NCBI's online tool, the Genetic Testing Registry (GTR), helps clinicians and patients navigate through the increasing use of genetic testing, as its role in improving drug safety and effectiveness becomes more commonplace.

Take a tour of the Genetic Testing Registry.

References

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