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Pharmacogenetics in personalised drug therapy

KRONIKK

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Pharmacogenetics can contribute to improved treatment and fewer adverse effects, but at present its application in clinical medicine is largely left to the individual doctor. How can we ensure equal treatment for all our patients in those cases in which pharmacogenetics has proved to be clinically useful?

The variation in drug-metabolising enzymes such as cytochrome P450 (CYP) and thiopurine methyltransferase first became clear in the 1980s (1, 2). It kindled hope that this knowledge could explain the inter-individual variation in drug responses. Laboratories introduced pharmacogenetic analyses, and some clinicians used this knowledge to personalise drug dosing (see Box 1 for explanation of terms). It has gradually been realised that factors other than genetic variants have a strong bearing on drug metabolism and final drug efficacy (3). The international medical community is now engaged in more targeted work to identify genetic variants that may lead to a direct therapeutic recommendation, in the form of either dose adjustment or selection of a different drug (4). There are already recommendations of this kind for some drugs and genetic variants, including some antidepressants and some proton pump inhibitors (5, 6). Before existing knowledge can be

implemented in routine clinical medicine, however, a number of challenges have to be overcome.

Box 1 Term explanations

Pharmacogenetics – the description of how variants of a gene may give rise to different responses to the same dose of a drug.
Pharmacogenomics – a broader term that describes how all the genes (the genome) may influence drug response. The terms *pharmacogenetics* and *pharmacogenomics* are often used interchangeably.
Pharmacokinetics – the description of the time course of drug absorption, distribution, metabolism and excretion.
Phenotype – characteristics that can be observed in an individual. In the case of CYP enzymes, the phenotype describes an enzymes capacity to metabolize a given substrate.

What do we know?

There are not many studies that have demonstrated that genotype-guided drug prescription yields superior therapeutic results, but there are some. For example, studies have shown that reduced activity of the CYP2D6 enzyme results in reduced conversion of codeine to morphine. The consequence for the patient is less effective pain-relief. In a Caucasian population, about 10 % of patients who are prescribed codeine will experience the same pain-relief effect from codeine as from a placebo (7), i.e. over 3 500 patients in Norway in 2017 (8). Nonetheless, there are no routine checks for reduced CYP2D6 activity. The cost-benefit value has not been adequately determined for this indication. The price level for analysis of a sequence variant is currently NOK 146 (see the reimbursement rate to public laboratories of the Norwegian Health Economics Administration (Helfo)), and the number of sequence variants investigated per gene has a bearing on the overall price.

There is a widespread misconception that different variants of a CYP enzyme are of significance for all drugs metabolised by the enzyme in question. However, it is difficult to predict the consequences of genetic variants on pharmacokinetics and clinical end-points on the basis of theoretical considerations. If one metabolic pathway is disabled, other pathways may take over to a greater or lesser extent. A change in the metabolite pattern may also influence efficacy. For this reason, the test results cannot be used to guide treatment with a particular drug until the clinical significance of a genetic variant is actually documented for that drug.

The gold standard for documentation of clinical usefulness is randomised controlled trials, and ideally this documentation is required to change established treatment guidelines. Several studies have shown that stented patients with acute coronary disease and reduced *CYP2C19* gene function are at greater risk of a further cardiovascular event when treated with clopidogrel than patients with normal *CYP2C19* function (9). The influential medical community is somewhat reluctant to introduce pharmacogenetic testing as a standard of care, nonetheless, and there is a demand for an even stronger evidence base for recommending this to the patient population (10). Currently in progress in several European countries is a prospective randomised study aimed at evaluating the impact of pharmacogenetically guided prescription of 41 drug-gene pairs on clinical outcomes and cost-effectiveness. The initial results are expected in 2020 (11).

In some cases, evidence with less strength, such as pharmacokinetic studies or retrospective studies, may be sufficient. One such case concerns variants of the *TPMT* gene, which is associated with thiopurine toxicity. There are no large, prospective randomised clinical trials, and for ethical reasons it will not be possible to perform such trials on the basis of existing data, as treatment with standard doses of thiopurines of patients with two

inactivating alleles of *TPMT* necessarily results in bone marrow suppression. Analysis of *TPMT* variants is currently being carried out on several patient groups for whom thiopurines are prescribed.

It can be difficult to translate genetic test results into clinical decisions. This was part of the background to the establishment in 2009 of the Clinical Pharmacogenetics Implementation Consortium, an international consortium whose purpose is to prepare the way for evidence-based use of pharmacogenetic analyses (4, 12). The consortium has published peer-reviewed dosing recommendations for gene-drug pairs where they find sufficient evidence for recommending a therapy based on genotype. The process of incorporating pharmacogenetic testing into clinical practice has come further in the USA than in Europe. Most large American hospitals that have implemented pharmacogenetics in clinical practice have chosen gene-drug pairs where such published therapeutic recommendations do exist (13). Examples of therapeutic areas for which recommendations exist are pain relief and treatment with proton pump inhibitors, antimycotics and antidepressants (6, 7, 14, 15).

Consensus terminology

The lack of standardisation makes clinical use of pharmacogenetics difficult, creates challenges with regard to the re-use of results and the use of results across different health services, and complicates the comparison of research results. The terminology used in pharmacogenetics is varied and not always uniform. Result reports from different laboratories contain different terms for describing variants, allele function and phenotype. The content of the reports also varies. Some laboratories report only genotype or phenotype, while others include lists of drugs that are affected by a given variant, with or without dosing recommendations. There is now a proposal for standardised English terminology (16, 17). The English terms should be adapted to Norwegian conditions, and our terms should be as close as possible to the international standardisation.

Analytical repertoire

When pharmacogenetic analyses are requested, the analyses offered will vary across laboratories. This means that different genes are included in laboratory-assembled "packages", but also that the sequence variants investigated for each gene may differ. The analytical repertoire consists mainly of the most frequently occurring genetic variants. Today's methods are designed to detect predefined variants, so only specifically targeted variants will be found. If none of these variants are detected, "normal" activity is reported. The lack of standardisation of analytical repertoires may lead to some laboratories finding variants that others are not looking for. Whether the analytical result is reported as normal activity or altered activity then depends on which laboratory is performing the analysis. Clinicians who request the analyses may not be aware whether relevant variants are included. This problem could be solved by reaching agreement on which variants there is a scientific basis for providing, and coordinating the analyses offered.

Information flow and decision-support tools

Ideally, pharmacogenetic test results can be used to guide future prescriptions. In order to achieve broad clinical implementation in those cases where pharmacogenetics is found to be useful, tools must be developed to make analytical results available in busy medical practices. The standard laboratory format of a single numerical result and associated reference range is not appropriate for reporting the results of pharmacogenetic analyses. The impact of a detected variant depends on the drug in question. Good decision-support tools are therefore important. In a hypothetical example, prescribing a new drug for a previously genotyped patient would trigger a warning if relevant variants were detected. Such systems are costly and time-consuming to develop. Ideally, this sort of information

should also be available across different electronic patient records that are in use.

Pharmacogenetic differences can explain much of the variation in the responses of individuals to drugs. However, the use of genotyping for individual dose recommendations must be supported by research showing that the results of treatment will be superior or the adverse effects fewer. For some drugs, there is only circumstantial evidence that genotyping may be useful, and it is important not to communicate unrealistically high expectations of pharmacogenetic analyses. For drugs where the clinical usefulness of pharmacogenetic analyses has been substantiated, systems must be developed to ensure that this knowledge benefits all patients.

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