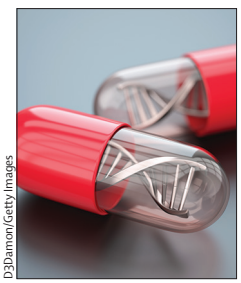
Clinical use of pre-emptive pharmacogenetic programmes



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The clinical implementation of pharmacogenetics (the study of how genetics influence individual variations in drug response) is a key factor in the development of programmes to prevent adverse drug reactions. Yet pharmacogenetics testing in clinics is still infrequent and is mainly reactive and focused on analysing a single drug–gene interaction. Evaluation of the implementation of pharmacogenetics in the real world is necessary. Only very few pilot studies have used a pharmacogenetics panel strategy to guide drug therapy, and mostly in patients aged over 65 years in specialised care settings in the USA. The results of these pilot studies appear promising, as decreases in hospitalisations, emergency department visits, and health-care costs were observed.[1–3]

Jesse J Swen and colleagues[4] did an open, multicentre, controlled, cluster-randomised, crossover implementation study of a 12-gene pharmacogenetics panel covering 42 drugs (following the Dutch Pharmacogenomics Working Group [DPWG] guidelines) deployed across seven European health-care systems to address the potential clinical effect of using pharmacogenetics for the prevention of short-term adverse drug reactions in real-world settings. 6944 adult patients (51·4% female, 48·6% male; median age 58·0 years, 97·7% self-reported European, Mediterranean, or Middle Eastern ethnicity, with a mean 7·88 [SD 6·6] co-medications) being treated with a drug with a clinical recommendation in the DPWG guidelines were enrolled. Participants received either genotype-guided doses (3342 [51·9%]) or standard care (3602 [48·1%]); however adherence to the DPWG recommendation was not mandatory and was left to the discretion of the treating physicians and pharmacists, but monitored). The study compared patients with an actionable drug–gene interaction test result (ie, a result for which the DPWG recommended a change to standard care drug treatment) in the intervention group (n=725) and in the control group (n=833) and reported that the risk of severe adverse drug reactions was reduced by 30% in the intervention group compared with in the control group (odds ratio [OR] 0·70; 95% CI 0·54–0·91; p=0·0075). Interestingly, when comparing all patients (n=2923 in the intervention group *vs* n=3270 in the control group), including those with actionable and non-actionable drug–gene interaction test results, the risk of an adverse drug reaction was also reduced by 30% (OR 0·70; 95% CI 0·61–0·79; p<0·0001). The study also highlighted that the covariant, number of concomitant medications, was associated with a significant increase in adverse drug reactions.

To our knowledge, the study was the first time that the influence of a pharmacogenetics programme in European health-care systems had been evaluated in the real world, with results that might lead to a change in clinical care. However, some aspects of the study need to be considered.

First, it would be very helpful to identify which adverse drug reactions were decreased by following the DPWG guidelines recommendations in relation to the result of each studied drug–gene pair. Although there was a reported overall decrease in adverse drug reactions, the relationship between implementing a particular genetic test for a given drug and the adverse drug reaction prevented was not shown. In support of this concern, a reduction in adverse drug reactions (in the intervention group *vs* in the control group) appeared to occur not only in the groups with actionable pharmacogenetic recommendations, but also in the groups with and without recommendations.[4] This perplexity might be associated with factors that are intrinsic to the prescribed intervention and independent of pharmacogenetic recommendations, such as increased care, treatment monitoring, and even behavioural factors associated with the genotype itself.[5] Nevertheless, the contribution of the pharmacogenetic factors might have been underestimated, considering that the study only included in its analysis one adverse drug reaction (the most severe), despite the possibility that there could be several. Furthermore, in the case of there being several prescribed drugs with actionable pharmacogenetics recommendations, only one drug was included for the analysis.[4]

For the future development of pharmacogenetics programmes to prevent adverse drug reactions in real-world settings, it will be necessary to determine the relationship between a pharmacogenetics recommendation and the decrease in a specific adverse drug reaction in a real-world case scenario that involves polytherapy and the influence of several genetic polymorphisms. Therefore, the interpretation of metabolic

phenotypes needs to be evaluated with consideration of drug–drug–gene interactions caused by polypharmacy. However, the majority of recommendations in the most widely used pharmacogenetic guidelines (eg, Clinical Pharmacogenetics Implementation Consortium[6] and DPWG[7]) are still based on single gene–drug pairs. A concomitant medication might change the recommendations for a given genotype because of phenocopy or phenoconversion,[8] so it is important to take into account genetic information and the influence of concomitant drugs when assigning the metabolic phenotype.[8] Indeed, phenocopy reflects the real enzyme metabolic capacity at the time of the study and hence is the clinically relevant capacity. Therefore, further research should consider estimating the metabolic phenotypes during polypharmacy, because a phenotype (metabolic capacity) calculated from a genotype can change (ie, from extensive to poor metaboliser status) and therefore the associated clinical recommendation can also change, owing to the influence of concomitant medications. Furthermore, the influence of several genes on pharmacokinetics, and therefore on adverse drug reactions, should be considered. Such considerations are supported by the results of a study[9] published in 2022, in which polypharmacy and the combined high metabolic capacity of two genes (*CYP2D6* and *CYP2C19*) involved in the metabolism of antidepressants were shown to increase the risk of suicide re-attempts, which can be also seen as a severe adverse drug reaction to be prevented.

Altogether, the study by Swen and colleagues[4] reports an association between the clinical implementation of a pharmacogenetics programme and a reduction in adverse drug reactions. However, for the future development of programmes to prevent adverse drug reactions the relationship between prescriptions based on genetics and the decrease in specific adverse drug reactions needs to be clarified. Furthermore, guidelines need to be developed that formulate recommendations in the context of polytherapy and the influence of several genes.

We declare no competing interests.

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Cardiovascular risk assessment in survivors of cancer

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Risk assessment has become pivotal in the prevention of cardiovascular disease. Risk prediction tools are intended to estimate prognosis in an unbiased and reliable way, and to provide objective outcome probabilities.[1] Although the use of such tools is recommended by European[2] and American[3] clinical practice guidelines, they are not adequately implemented in clinical practice. In New Zealand, risk assessment for people aged 30–74 years without a history of cardiovascular disease is now based on the 5-year cardiovascular disease risk prediction equations derived from the New Zealand cohort of the PREDICT study.[4] This risk tool has been embedded in decision support software across primary care settings. In addition to providing probabilities of fatal and non-fatal outcomes, this tool also provides guidance for management, as patients should be managed differently according to their risk category.

Survivors of cancer are at an increased risk of cardiovascular disease, not only because of their exposure to cardiotoxic therapies but also because of the