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.

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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


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presence of concomitant cardiometabolic risk factors (insulin resistance, obesity, and tobacco exposure are associated with both the cancer and cardiovascular disease pathways), advanced age (cancer is largely a disease of ageing), and a decrease in patients' adherence to medications (eg, statins) for non-cancer conditions during or soon after active cancer therapy. Most of these factors are directly or indirectly included in risk calculators for the general population; however, the validity of traditional risk prediction tools in survivors of cancer had not been robustly validated. To date, some evidence has been provided by small studies of specific cancer types.[5] The paucity of research into cardiovascular disease risk prediction tools among survivors of cancer has not yet met the clinical need.

In this issue of *The Lancet*, Essa Tawfiq and colleagues present an open cohort study to assess the performance of cardiovascular disease risk prediction equations in a large population of survivors of cancer in New Zealand.[6] The aim of the study was to validate the existing prediction model for primary care patients in a sub-cohort (patients with cancer) of the original PREDICT cohort. In a large population of 14 263 survivors of cancer (57% women and 43% men) with broad age representation (mean age 60·5 years [SD 8·5]) and several self-identified ethnicities (mostly European [79%] but also Māori, Pacific, Indian, and Chinese or other Asian ethnicity), the model showed moderate discrimination (Harrell's C statistic was 0·67 for men and 0·73 for women) and relatively good performance across three clinical risk groups of 5-year risk (<5%, 5% to <15%, and ≥15%). The three clinical risk groups were defined on the basis of clinically meaningful cutoffs. If the 5-year risk of cardiovascular disease is less than 5% only lifestyle advice is recommended, whereas if this risk is at least 15% both medication and lifestyle advice are strongly recommended. For people with a 5-year risk of between 5% and less than 15%, the initiation of cardiovascular disease medication management can also be considered in addition to lifestyle advice.

This study fills a gap in evidence by showing a reasonably good performance of the model in a population of patients for whom the prediction of cardiovascular disease outcomes had been neglected.[7] Importantly, the tool provides sex-specific assessment. The broad implementation of the risk equation and its implications for clinical decision making are other strong points of the study. However, the two main weaknesses of such a great effort to cover this unmet clinical need should be discussed. First, discrimination performance is moderate at best. Harrell's C statistics for both men and women suggest a large overlap between scores (predicted probabilities) in patients with and without the outcome. In the ideal situation—a C statistic of 1—all participants with the outcome would have a higher score than any given patient without the outcome. In this study, a higher score does not necessarily translate into a higher risk of events (particularly for men, for whom the C statistic was 0·67). The obvious reason for this suboptimal performance is the inherent nature of the predicted outcome. Whereas death is an unambiguous event that does not often occur randomly, non-fatal events (eg, hospitalisation) happen more at random, and are therefore less easy to predict than death.[8] The other main limitation of the study is the failure to account for competing risks of death, which are of course very relevant for survivors of cancer. A competing risk could prevent the event of interest from taking place (eg, a person who dies of cancer is no longer at risk of death from cardiovascular disease).[9] Although the 5-year cardiovascular disease risk prediction equations were developed for a general population in which competing mortality risks were not a major issue,[9] the increased mortality risk for survivors of cancer compared with primary care patients without a history of cancer should be acknowledged.

Other, less relevant limitations of the study could be the long recruitment period (1996–2016 for cancer diagnosis and 2002–18 for cardiovascular disease risk assessment) and the absence of cancer-specific predictors.[10] The long recruitment period is relevant because considerable advances in the medical management of both cancer and cardiovascular diseases have occurred during these periods,[11] and the lack of cancer-specific predictors is relevant because each cancer type has a different prognosis. Substantial heterogeneity therefore exists in the underlying risk of the study population.[10]

Understanding how well an implemented prediction model performs in already heterogeneous populations (eg, to what extent the existing risk prediction models can broadly predict cardiovascular disease risk in survivors of all types of cancer) is of interest to clinicians.

Model performance is of particular importance for doctors in New Zealand, in which the study was based, because of the implications for clinical management. To provide less biased estimates and more accurate predicted probabilities, future research should focus on addressing potential competing risks (or alternatively, predicting all-cause mortality) and exploring cancer-specific predictors, such as the type of cancer, its stage, and its treatment.[10] Considering these factors would generate new risk assessment tools to better predict cardiovascular outcomes. Survivors of cancer would fall more often into the adequate risk category, and this would be translated into adequate clinical management.

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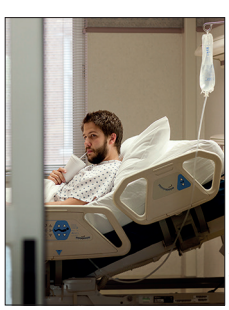
Postoperative antibiotics can be de-escalated after laparoscopic surgery for complex appendicitis

Appendicitis is the most common surgical emergency globally, and surgery remains the mainstay of treatment in more than 98% of cases.[1,2] However, variations in management are extremely common and are under-researched. For example, there is little agreement over the best preoperative diagnostic strategy, the role of antibiotics as a primary treatment, and how to best implement laparoscopic appendicectomy in low-income and middle-income countries. Evidence regarding the duration of antibiotics after surgery is scarce, and cautious behaviours tend to result in longer courses being prescribed. Postoperative antibiotics are justified if they reduce complications; otherwise, they exacerbate costs, increase antimicrobial resistance, delay discharge from hospital, and have a carbon consequence.

The pragmatic APPIC trial addressed 5 days versus 2 days of antibiotics after appendicectomy for complex appendicitis.[3] In 1066 randomly assigned patients, the adjusted absolute risk difference was 2·0% in a composite endpoint of infectious complications and mortality within 90 days of surgery, in favour of the 5-day group. This was a non-inferior finding, as the 95% CI was wide (−1·6% to 5·6%), meaning that 2-day courses have similar outcomes in these patients and in this setting. For these patients, of whom 89% were adults (aged ≥18 years) and 43% were female, context is important. The fact that 95% of patients underwent laparoscopic surgery is indicative of a health system that facilitates earlier patient presentation, better preoperative capacity to diagnose, and the ability to identify and treat postoperative complications. Taken together, the findings suggest that giving shorter courses of antibiotics is safe and should be adopted in patients who have laparoscopic appendicectomy. Subgroup analysis suggested that the small number of patients who had open surgery, including laparoscopic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