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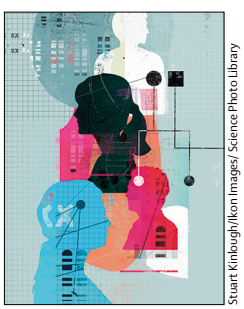
Assessment of breast cancer risk: which tools to use?



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Risk-assessment tools are used in routine clinical practice to identify women at increased risk of breast cancer and to inform counselling about lifestyle changes, genetic testing, screening timing or modality, and eligibility for risk-reducing drugs or surgery. In *The Lancet Oncology*, Mary Beth Terry and colleagues[1] report a comparative validation of four models—the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm model (BOADICEA), BRCAPRO, the Breast Cancer Risk Assessment Tool (BCRAT), and the International Breast Cancer Intervention Study model (IBIS)—used in clinical practice to provide absolute risk estimates for breast cancer on the basis of different sets of factors. Their work is an important contribution to the field in view of the need for robust, comparative assessments of risk models. Terry and colleagues assessed model calibration with data from a combination of family-based cohorts in Australia, Canada, and the USA—the Breast Cancer Prospective Family Study Cohort. In this study population, BOADICEA and IBIS were the best-performing models in terms of calibration and risk discrimination. Although the study population was large (15 732 women without breast cancer at baseline, 619 of whom developed invasive breast cancer within 10 years of follow-up), important subgroup analyses by country or by age and mutation status were limited by size. 5-year and 10-year risk estimates were well calibrated overall, but both models overpredicted risk in women in the highest risk quantile for breast cancer. This overprediction was small (eg, the predicted *vs* observed 10-year risk of breast cancer in *BRCA*-negative women was 7·1% *vs* 6·1% for BOADICEA and 7·5% *vs* 6·5% for IBIS). However, the highest risk quantile included both moderate-risk and high-risk women (ie, women with a 10-year risk ≥5% or a 5-year risk ≥2·5%), and thus might not fully reflect prediction accuracy in women at high risk of breast cancer. It is also important to assess model performance in several independent study populations because both model calibration and risk discrimination are population dependent. Consistent with findings in the Breast Cancer Prospective Family Study Cohort,[1] two other reports[2,3] based on large prospective cohorts in the USA and the UK have shown overprediction of breast cancer risk in women at high risk, showing that further model improvements are needed. These studies mostly included non-Hispanic white women, similar to the make-up of the Breast Cancer Prospective Family Study Cohort. Other racial and ethnic groups have been traditionally understudied, but efforts by different groups are underway to address this important research gap.

Simpler models, such as BCRAT, are sometimes preferred over complex models because they are easier and faster to use. However, the consequence of this simplicity is lower risk discrimination at the population level and less accurate risk scores for individual women. Although differences in measures of risk discrimination, such as the concordance statistic used by Terry and colleagues,[1] might be small, more comprehensive information about risk factors could substantially improve the ability to identify women at high or low extremes of risk. For instance, a personal history of atypical hyperplasia, lobular carcinoma in situ, or high mammographic breast density can place women in the high-risk category, but these risk factors were not assessed by Terry and colleagues because of data limitations. Polygenic risk scores, which are derived from genetic testing of many common genetic variants, are a new, important risk factor for breast cancer. Although the variants are associated with small risks individually, when aggregated as a polygenic risk score, they can identify women with or without a family history of breast cancer at substantially different levels of risk.[2,4-6] Both IBIS and BOACIDEA have been extended to include information on polygenic risk (although this information was not included in the versions analysed by Terry and colleagues),[5,7] and clinical tests to measure

polygenic risk scores are already available. However, there is an urgent need for both rigorous assessment of the calibration of risk scores based on integration of polygenic risk scores and other known risk factors (such as family history, lifestyle, or benign breast disease), and training of health-care providers on how to interpret results.

Ideally, risk assessment tools should be flexible and easy to update as and when new data about risk emerge, and should be able to accommodate for missing data to predict risk on the basis of a subset of risk factors.[6,8,9] Furthermore, the complexity and heterogeneity of disease might necessitate risk stratification by subtype.[10] User-friendly interfaces for risk assessment and communication tailored to specific clinical scenarios could facilitate the use of complex underlying risk models and provide guidance to users. Such an approach would also address the challenge of choosing from the available models without a clear understanding of the pros and cons of each one.

In summary, application of clinical guidelines and progress towards new precision prevention strategies (eg, risk-stratified screening strategies that are being assessed in trials) requires the development of flexible, comprehensive models with robust validation in diverse populations to provide accurate personalised risk estimates, particularly in women at high risk of cancer, for whom clinical decisions have the greatest potential impact. Furthermore, when possible, models should be validated in the populations in which they are intended to be used—eg, in health-care delivery settings.

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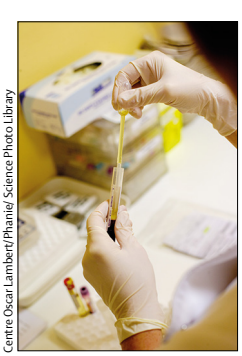
Precision oncology giveth and precision oncology taketh away



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Efforts to improve outcomes for cancer patients often centre on molecular profiling of individual tumours to identify actionable mutations and alterations that allow doctors to tailor treatment to the individual patient. Although it is preferable to find an inclusionary marker—a particular molecular vulnerability that supports the use of a treatment that would otherwise not have been considered—exclusionary markers, mutations, or amplifications that preclude activity of an otherwise standard and seemingly reasonable treatment strategy, are also encountered. *RAS* mutations in colorectal cancer are a good example of an exclusionary marker, since the presence of a *RAS* mutation excludes the realistic possibility of benefit from an anti-EGFR monoclonal antibody and therefore precludes the use of anti-EGFR therapies in practice, thus sparing the patient the toxicity, expense, and false hope of a treatment that doctors know in advance will not work. Although inclusionary markers are preferred, both types of markers can improve the quality of patient care.

In this issue of *The Lancet Oncology*, Funda Meric-Bernstam and colleagues,[1] investigators of the MyPathway study, present updated data regarding the targeting of *HER2*-amplified colorectal cancer with a combination of two anti-HER2 drugs, pertuzumab and trastuzumab. The finding of anti-tumour activity