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Polygenic risk scores in cancer screening: a glass half full or half empty?

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Current cancer screening programmes use age and sex to define the individuals most likely to benefit. However, cancer risk also varies widely between people according to their genetics, lifestyle, and other risk factors. The principle of risk-stratified screening, beyond age and sex, is already incorporated into guidelines by the National Institute for Health and Care Excellence (NICE)[1] and others, for example through offering enhanced breast cancer screening to women with a family history of breast cancer. Polygenic risk scores (PRSs) represent the combined effect of multiple genetic variants on cancer risk , identified through genome-wide association studies (GWASs), and provide a powerful risk prediction approach with the potential to identify many more individuals at high or low cancer risk than is possible on the basis of age alone. In this regard, PRS have shown promise in providing personalised risk prediction and informing cancer screening strategies.[2,3] Combining PRS with age and other risk factors would allow for improved risk stratification for risk-targeted and risk-tailored cancer screening.[4]

In *The Lancet Oncology*, Catherine Huntley and colleagues[5] model the outcome of hypothetical screening programmes in terms of cancer detection and cancer deaths averted, by initiating or extending screening for several cancers, including breast (for women aged 40–49 years), colorectal (for individuals aged 50–59 years), and prostate cancers (for men aged 60–69 years) to individuals with a high PRS. The authors found a small increase in the numbers of deaths averted if screening were to be extended to high-risk individuals (which they defined as the 20% of individuals with the highest PRS), compared with screening of the oldest 20%, with a corresponding smaller number of individuals needed to be screened for 10 years per one death averted. Although their analysis suggests only a modest potential efficiency gain if PRS alone were used to identify high-risk individuals for screening, it does not reflect the only or even the most probable way in which PRS could be used. In particular, rather than considering age and PRS as mutually exclusive options, it is more rational to consider stratification based on a combination of age and PRS, and the absolute risk of cancer. In practice, stratification can also be considerably improved by combining PRS with other risk factors (notably family history and, for breast cancer, breast imaging markers).[4]

Huntley and colleagues focused on providing additional screening to the PRS-defined high-risk group, but there are several other ways in which risk-stratified screening might be used—most importantly, by providing less intensive screening to low-risk individuals (to reduce the unnecessary harms and costs of overscreening) and tailoring screening age range, frequency, and method to each risk group. The benefit–harm balance, cost-effectiveness, and implementation of a risk-stratified screening programme would vary with each screening approach and would need to be evaluated through modelling approaches, in combination with trials. There are already several ongoing studies on the implementation of risk-stratified

screening programmes[6,7] and personalised breast cancer screening randomised trials.[8,9] These studies will generate empirical evidence on the utility of risk stratification in population-based screening programmes on which national screening policies can be based.

Overdiagnosis—the detection of cancer that would not have presented symptomatically in a person's lifetime in the absence of screening—is an important consideration of any screening programme. Although overdiagnosis occurs with screen detection of indolent cancers, it also occurs with detection of a progressive cancer with a lead-time longer than the remaining life expectancy of an individual.[10] Risk assessment and tailoring the screening frequency and age range of screening could reduce overdiagnosis and improve the benefit–harm balance of screening. Studying the utility of PRS in a screening programme requires modelling these intricacies. Robust data and robust models are needed to evaluate different approaches of risk-stratified screening programmes.

Huntley and colleagues correctly point out that there are inherent limitations to the predictive value of PRS. However, all medical advances have limitations, and just because the predictive value has limits, does not mean it is not worth pursuing. Current cancer screening programmes also have limitations and are expensive programmes to deliver; therefore, it is important to continue to try and improve their effectiveness. The use of PRSs in informing screening strategies of common cancers is promising, but, nevertheless, the additional complexity that would be introduced to screening programmes should be acknowledged and the best way to use this information identified. These complexities should not discourage the pursuit of risk-stratified screening approaches, rather the scientific community, health-care providers, policy makers, and the public have to work together to identify the best ways to implement screening programmes that could improve the benefit–harm trade-offs, cost-effectiveness and acceptability to users and providers, and feasibility of implementation, as well as equity of access.

Conflicts of Interest:

DFE received payments to their institution for the licensing of the BOADICEA/CanRisk risk prediction algorithm. All other authors declare no competing interests.

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