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.

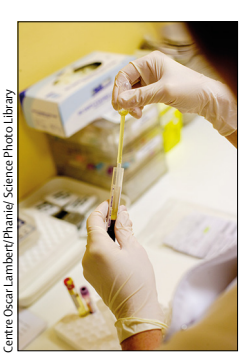
In summary, application of clinical guidelines and progress towards new precision prevention strategies (eg, risk-stratified screening strategies that are being assessed in trials) requires the development of flexible, comprehensive models with robust validation in diverse populations to provide accurate 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.

Montserrat Garcia-Closas, Nilanjan Chatterjee
Division of Cancer Epidemiology and Genetics, National Cancer Institute, Shady Grove Campus, Rockville, MD 20850 (MG-C); and Bloomberg School of Public Health and Department of Oncology, School of Medicine, Johns Hopkins University, Baltimore, MD, USA (NC)
montserrat.garcia-closas@nih.gov

We declare no competing interests.

1 Terry MB, Liao Y, Whittemore AS. 10-year performance of four models of breast cancer risk: a validation study. *Lancet Oncology* 2019; published online Feb 21. http://dx.doi.org/10.1016/S1470-2045(18)30902-1.
2 Choudhury PP, Wilcox AN, Brook MN, et al. Comparative validation of breast cancer risk prediction models and projections for future risk stratification. bioRxiv 2018; published online Oct 19. DOI:10.1101/440347.
3 Brentnall AR, Cuzick J, Buist DSM, Bowles EJA. Long-term accuracy of breast cancer risk assessment combining classic risk factors and breast density. *JAMA Oncol* 2018; **4:** e180174.
4 Mavaddat N, Michailidou K, Dennis J, et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *Am J Hum Genet* 2019; **104:** 21–34.
5 Cuzick J, Brentnall AR, Segal C, et al. Impact of a panel of 88 single nucleotide polymorphisms on the risk of breast cancer in high-risk women: results from two randomized tamoxifen prevention trials. *J Clin Oncol* 2017; **35:** 743–50.
6 Maas P, Barrdahl M, Joshi AD, et al. Breast cancer risk from modifiable and nonmodifiable risk factors among white women in the United States. *JAMA Oncol* 2016; **2:** 1295.
7 Lee A, Mavaddat N, Wilcox AN, et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. *Genet Med* 2019; **31:** 33.
8 Choudhury PP, Wilcox AN, Wheeler B, et al. iCARE: an R package to build and apply absolute risk models. *bioRxiv* 2016; published online Oct 12. DOI:10.1101/079954.
9 Grill S, Ankerst DP, Gail MH, Chatterjee N, Pfeiffer RM. Comparison of approaches for incorporating new information into existing risk prediction models. *Stat Med* 2017; **36:** 1134–56.
10 Li K, Anderson G, Viallon V, et al. Risk prediction for estrogen receptor-specific breast cancers in two large prospective cohorts. *Breast Cancer Res* 2018; **20:** 147.

Precision oncology giveth and precision oncology taketh away



Centre Oscar Lambret/Phanie/ Science Photo Library

Published Online
March 8, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30095-6

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

is confirmatory of a previous study[2] showing that 30% of patients with colorectal cancer with *HER2* overexpression and wild-type *KRAS* achieved a response when treated with another dual anti-HER2 therapy, combining lapatinib plus trastuzumab. Meric-Bernstam and colleagues[1] chose to study patients with *HER2*-amplified colorectal cancer regardless of *KRAS* status, and for statistical consistency they report their primary outcome (the proportion of patients achieving an objective response) in their prespecified, *KRAS*-independent, primary cohort. In this patient population, 18 (32%, 95% CI 20–45) of 57 patients achieved an objective response to treatment with pertuzumab and trastuzumab. The most informative result, however, is the secondary analysis of activity as a function of *KRAS* mutation status. 17 (40%, 95% CI 25–56) of 43 patients with *HER2* amplification and wild-type *KRAS* achieved a response and the median duration of response was just over 6 months (6·1 months, 95% CI 2·9–11·1). However, in the 13 patients with *KRAS* mutations the activity was negligible, with only one (8%, 0–36) patient achieving a response, which only lasted for 2·7 months.

The authors' stated conclusion is that activity was that "patients with *HER2*-amplified, *KRAS* wild-type metastatic colorectal cancer derive a greater benefit from pertuzumab plus trastuzumab than those with *KRAS*-mutated metastatic colorectal cancer".[1] I would respectfully suggest that this interpretation, although accurate, is an understatement. My interpretation is that clinically meaningful activity was shown exclusively in the *KRAS* wild-type population. An isolated trial of a regimen that showed response in one of 13 patients with a median progression-free survival of less than 3 months would not be considered as positive, or even encouraging. Treatment of patients with *HER2*-amplified but *KRAS*-mutated tumours with pertuzumab plus trastuzumab would thus be unsupported by the data, and would engender false hope, unwarranted exposure to toxicity, and an unnecessary financial burden for the patients; responsible stewardship of resources requires the medical community to consider that the average sales price in the USA for the drugs administered in this regimen in the first 6 weeks alone would currently be just over US$26 600 for a patient weighing 75 kg.[3]

It is well established that to properly treat a patient with metastatic colorectal cancer we must know their *KRAS*, *NRAS*, *BRAF*, and mismatch-repair (or microsatellite-instability) status. Arguably, *HER2* amplification status can now also be considered clinically relevant in metastatic colorectal cancer. It should be noted, however, that in earlier-stage, non-metastatic colorectal cancer, a use for these markers in the adjuvant setting has yet to be found, except for mismatch-repair deficiency being an exclusionary marker for treatment of stage II disease. However, in metastatic colorectal cancer, *HER2* amplification seems to be an actionable marker in both an inclusionary and exclusionary manner. A recent report by Raghav and colleagues[4] confirmed the exclusionary nature of *HER2* amplification in regards to anti-EGFR therapy in colorectal cancer, since patients with *HER2*-amplified colorectal cancer did not benefit from anti-EGFR-targeted therapies. A precision oncology treatment paradigm that includes consideration of *HER2* amplification would therefore suggest that anti-EGFR monoclonal antibodies have clinical utility in metastatic colorectal cancers that are *RAS* wild type, *BRAF* wild type, and not *HER2* amplified, albeit at substantial financial cost. Conversely, dual anti-HER2 strategies, either with lapatinib plus trastuzumab or pertuzumab plus trastuzumab, have moderate activity in the small subset of patients with metastatic colorectal cancer whose tumours are both *RAS* (and most probably also *BRAF*) wild type and *HER2* amplified. How and when to sequence these regimens, and what to offer to patients whose molecular profile indicates that they will not benefit, or to those who have progressed after receiving these treatments, remains the focus of intense investigation. The work in *HER2*-amplified colorectal cancer represents progress, but this progress is more modest than we would have hoped for from precision oncology, has high financial costs, and is not sufficient. Patients need and deserve better, and a lot of work still needs to be done.

See **Articles** page 518

Leonard B Saltz
Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA; and Weill Cornell Medical College, New York, NY, USA
SALTZL@mskcc.org

I report grants from Taiho Pharmaceuticals, outside the submitted work.

1 Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for *HER2*-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a multiple basket study. *Lancet Oncol* 2019; published online March 8. http://dx.doi.org/10.1016/S1470-2045(18)30904-5.

2 Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016; **17:** 738–46.

3 Centers for Medicare & Medicaid Services. 2019 ASP Drug Pricing Files. 2019. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2019ASPFiles.html (accessed Jan 26, 2019).

4 Raghav K, Loree JM, Morris JS, et al. Validation of *HER2* amplification as a predictive biomarker for anti–epidermal growth factor receptor antibody therapy in metastatic colorectal cancer. *JCO Precis Oncol* 2019; published online Jan 22. DOI:10.1200/PO.18.00226.

Adolescents and young adults with cancer and the risk of subsequent primary neoplasms: not just big children

Vision/Phanie/Science Photo Library

Published Online
February 20, 2019
http://dx.doi.org/10.1016/S1470-2045(18)30941-0

See Articles page 531

Improved outcomes in childhood cancer have led to an increased focus on the cost of long-term survival: long-term physical, psychological, and financial morbidities that arise as a consequence of cancer therapy or the cancer itself. Several landmark childhood cancer survivor cohorts have informed our ability to describe, predict, and minimise these late effects.[1,2] About 80% of adolescents and young adults (AYAs) with cancer will also achieve long-term cure.[3] Consequently, late effects are also highly relevant to this population, but very few AYA-specific data exist, forcing clinicians to extrapolate from the literature on childhood cancer survivors. Subsequent primary neoplasms (also known as second malignant neoplasms) are one of the most feared late effects, and are associated with substantial morbidity and mortality. Previous work has shown that survivors of AYA cancer have a higher absolute risk of subsequent primary neoplasms than do younger or older populations, which in turn has a substantial impact on overall survival.[4,5]

In *The Lancet Oncology*, Chloe Bright and colleagues[6] describe the risk of subsequent primary neoplasms in a population-based cohort of more than 200 000 survivors of AYA cancer. The large sample size and more than 2·6 million person-years of follow-up allow the investigators to describe, comprehensively for the first time and in great detail, the risk of specific subsequent primary neoplasms after specific primary cancers. The cumulative incidence of any subsequent primary neoplasm at 35 years from diagnosis ranged from 11·9% in survivors of breast cancer to 26·6% in female survivors of Hodgkin lymphoma. The level of granularity provided in the risk estimates (eg, by primary cancer, type of subsequent primary neoplasm, and years from diagnosis) should assist clinicians and policy makers in determining what type of interventions would be of greatest benefit for specific populations of AYA cancer survivors.

Beyond improving risk prediction, several implications of the data are worth highlighting. The results illustrate the dangers of applying findings from childhood cancer survivors to the AYA population. For example, the surprising burden of subsequent lung cancers stands in contrast to the childhood cancer literature.[7] In male survivors of Hodgkin lymphoma, lung cancer accounted for approximately 40% of the total number of excess subsequent primary neoplasms, with a cumulative incidence of lung neoplasms of 5·1% at 35 years from diagnosis. Substantial incidences were also seen in other survivor groups. It is unclear whether this difference compared with childhood cancer survivors is caused by several primary AYA cancers being themselves related to smoking history (eg, cervical cancer), a higher probability of smoking after diagnosis,[8] increased use of treatments such as lung radiotherapy, greater attained age, or a combination of these factors. Irrespective of the mechanism, Bright and colleagues' results support smoking cessation interventions for survivors and raise the intriguing question of whether lung cancer screening guidelines developed for other high-risk populations may be appropriate.[9]

A second difference concerns temporal trends. The risk of subsequent primary neoplasms in childhood cancer survivors has decreased over consecutive cohorts, largely associated with reductions in radiotherapy doses.[2,10] In this study, treatment decade was not significantly associated with subsequent primary neoplasm risk, suggesting that no such decline has occurred in the AYA survivor population. The reasons for this finding are unclear. AYA treatment intensity