Multi-cancer early detection tests: a strategy for improvement

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Current cancer screening strategies have evolved over the last several decades. For example, colorectal cancer (CRC) screening no longer relies solely on colonoscopy; patients now have the option of less invasive techniques, such as the stool-based faecal occult blood test and faecal immunochemical test, or the more invasive flexible sigmoidoscopy which can be completed without anaesthesia.1 2 Other United States Preventative Services Task Force (USPSTF) cancer screening recommendations (e.g., mammography or low-dose CT) require significant patient burden. Furthermore, there are ongoing debates on the utility of additional screening and surveillance strategies for those at increased risk of cancer. With an array of screening modalities—for individual cancers, occurring at different surveillance intervals—it can be difficult for patients to keep track of, and thus adhere to, cancer screening. Research suggests that when patients are offered a choice of screening modalities the likelihood of screening is reduced, and that patients who discuss multiple screening types with their physician are more likely to be confused about screening than those who only discuss one option, which is also associated with non-adherence.3 4 Therefore, simplifying screening options and delivery may improve patient adherence.

The transition to minimally invasive screening modalities has proven difficult and options are currently limited. For instance, urinary bladder tumour antigen and NMP22 assays have been approved by the US Food and Drug Administration (FDA) for monitoring bladder cancer progression, but only in combination with cystoscopy.5 6 Methylated SEPT9 has been touted as a promising blood-based diagnostic marker for CRC, with high blood-based sensitivity and specificity,7 however this test is not currently recommended by the USPSTF for screening and detection. Despite the advancement of minimally invasive techniques for detection, most biomarkers, and biomarker panels, detect the presence of a single cancer, thus not truly reducing screening burden. A way to mediate this issue is through the advent of multicancer early detection (MCED) tests, which aim to detect the presence of several cancer types in people without symptoms using a single test, with the hope of early intervention. The ideal scenario for cancer screening and early detection would be that all people without symptoms and/or those of average risk could provide a blood sample and use an approved MCED; if positive, the person would see their provider to determine the appropriate follow-up steps, though limitations in assay development and follow-up protocols need to be addressed. A sole example combating these concerns is the SYMPLIFY study—the first large-scale prospective assessment of an MCED. This study, which is a collaborative effort between the National Health Service (United Kingdom) and GRAIL, seeks to test the utility and feasibility of MCEDs at a population scale.8

A new take on MCEDs, explored in this issue of BMJ Oncology by Budnik and colleagues, to improve on the problem of sensitivity and specificity may be to develop a targeted MCED for population subsets.9 A means to accomplish this may be by generating, and employing, a sex-specific cancer detection panel. Using a case-control study design, Budnik and colleagues demonstrated high sensitivity for cancer detection in men and women at 99% specificity and early stage, as well as accurate identification of tissue of origin for over 80% of cases. There are several arguments to support sex-specific cancer detection methods. Women have higher rates of invasive cancers at earlier ages than men.10 Though there are similarities among the most common cancers diagnosed in men and women in the United States, there are also important differences, with breast and uterine among the top 10 diagnosed cancers in women and prostate in men.10 Additionally,
gender disparities exist in cancer diagnoses; for example, larynx, hypopharynx and bladder have the highest male-to-female cancer incidence ratios globally, and anal and thyroid cancers have the lowest.11

Further rationale for sex-specific MCEDs are demonstrated genetic differences by sex for some cancer types. For example, germline TP53 mutations are associated with increased cancer incidence and earlier onset age in women compared with men.12 In acute lymphoblastic leukaemia, deletion of GSTTI and a C>T polymorphism in NQO1 was associated with increased incidence in men, but not in women.13 Additional sex-specific differences have been observed for overall mutational burden, copy number alterations, and methylation patterns. Lastly, recent research suggests that the X chromosome may impact overall mutational burden, as the X chromosome encodes several genes with roles in tumour suppression, epigenetic regulation, and interactions with the p53 pathway. For instance, loss of heterozygosity on the X chromosome at p22.2–3 and p25–26 is associated with ovarian cancers with germline BRCA1 and TP53 loss, among other genes including FOXP3 (Xq26.1) and ELF4 (Xp11.23).14

Although several problems need to be addressed before MCEDs can be deployed at a population scale, a method to improve on current issues of sensitivity and specificity may be use of sex-specific detection panels, as shown in the study by Budnik and colleagues. As discussed, demonstrable sex-specific differences in cancer—including age of onset, cancer types and genetic alterations—suggest this approach would be useful. The widespread use of MCEDs may be a way down the road, but perhaps employing a strategy like sex-specific MCED panels could get the field moving a little faster.

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