



83%, the cancer site was within the top two predicted locations. The accuracy of the predictions varied by tumour type, and was high for colorectal, ovarian, and pancreatic cancers (~80%), but markedly lower for upper gastrointestinal, liver, and lung cancers (~40%). “The ability to accurately detect the tumour location is a major step forward,” states Lennon.

The prospect of early cancer detection using an affordable, non-invasive test is exciting; however, further studies are needed to establish the diagnostic potential of such liquid biopsy screening tests in the general population. In this regard, the authors emphasize that the individuals included in their study had mostly been diagnosed with symptomatic cancer. Asymptomatic individuals will probably have earlier-stage disease, for which the sensitivity of detection is likely to be lower: the median sensitivity for stage II–III cancers was 73–78%, but was only 43% for stage I disease (although ranging from 20% for oesophageal cancer to 100% for liver cancer). Incorporation of other biomarkers, such as metabolites, microRNAs, and methylated DNA, might increase the sensitivity of the test and refine predictions of cancer location. Another concern is that the specificity of the test could be lower in ‘real world’ populations that include individuals with comorbidities, such as inflammatory disease, which might increase the risk of false positives.

Importantly, the researchers now plan to validate CancerSEEK prospectively in a large-scale study comprising individuals without a cancer diagnosis. “Our ultimate vision is a non-invasive blood-based test that can be used to screen for multiple common types of cancer in asymptomatic, apparently healthy individuals,” Lennon concludes.

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Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*  
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Improvements in early cancer detection are key to increasing eligibility for curative treatments and thereby reducing the incidence of cancer-related death. However, few screening tests exist for individuals with an average risk of cancer, and those that do exist focus on one cancer type, and are invasive and/or expensive. Liquid biopsy approaches hold promise in the non-invasive detection of cancer, but sensitivity is an issue. A new approach called CancerSEEK addresses many of these limitations and paves the way for a broadly applicable liquid biopsy screen for multiple cancer types.

CancerSEEK involves “the use of a unique, non-invasive, multi-analyte test that simultaneously evaluates the presence of mutations and eight cancer-associated protein biomarkers in blood,” explains co-developer Anne Marie Lennon. Multiplex PCR analysis of circulating cell-free tumour DNA (ctDNA) enables the detection of mutations at 2,001 genomic positions across 16 genes, whereas levels of the protein biomarkers are assessed using immunoassays. “Although each marker does not have sufficient sensitivity to be used alone to detect cancer, the multi-analyte approach markedly increases the test sensitivity,” Lennon adds.

CancerSEEK was used in 1,005 patients previously diagnosed with stage I–III breast, colorectal, gastric, liver, lung, oesophageal, ovarian, or pancreatic cancer. Notably, these eight

cancer types accounted for 60% of the estimated cancer-related deaths in the USA in 2017. A median of 70% of the 1,005 patients tested positive for cancer according to CancerSEEK, with sensitivities of detection that ranged from 33% for breast cancer to 98% for ovarian cancer; the sensitivity was >69% for the five cancers (ovarian, liver, gastric, pancreas and oesophageal) for which no routine screening modalities are currently available.

The specificity of CancerSEEK was >99%, with only 7 of 812 control individuals testing positive. High specificity is important to prevent unnecessary follow-up interventions and psychological distress associated with false-positive results. “Unlike other liquid biopsy studies, we specifically used a small, robust panel, which minimized the risk of false-positive results; the use of a small panel also decreases costs, ensuring that the test remains affordable,” says Lennon.

Detection of cancer alone is not sufficient: localization of the cancer is another critical component of screening tests. Liquid biopsies of ctDNA typically have limited utility in this regard because most of the analysed mutations occur across a range of cancers. By contrast, application of a supervised machine-learning algorithm to the multi-analyte data enabled the organ of origin to be correctly identified in a median of 63% of the patients with a positive CancerSEEK test, and in a median of

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