New Blood Test SEEKs To Detect and Localize Cancer before It’s Too Late

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The key to the management and cure of most solid tumors is being able to rapidly identify and treat early stage disease. In most cases, if the presence and location of cancer cells can be determined prior to migration from the primary tumor to regional (lymph node metastasis) or distant (organ metastasis) locations, there is a relatively high probability that cure can be achieved through surgery and/or radiation/chemotherapy. Given the high value of early detection, there remains a pressing need for sensitive and selective tests that can detect these early stage malignancies.

Conventional imaging strategies for the diagnosis of cancer typically rely on anatomic (computed tomography and magnetic resonance) and metabolic imaging methods (positron emission tomography) combined with some definitive diagnostic procedure for pathological confirmation (i.e., cytology or biopsy). These imaging strategies usually rely on some prior knowledge of the location of a cancer lesion and/or are effective for disease only over a centimeter or so in size. For many cancers, disease pathology begins only after a preneoplastic lesion progresses to aggressive growth and metastasis, in a process that can sometimes take decades. Recent advances in our knowledge of the evolution of cancer suggest that early detection is the key to finding effective cures for diverse cancer types. However, early detection requires methods that are relatively inexpensive, simple, non-invasive, and fast so that they can be performed on a regular basis without the need for extensive medical supervision and/or infrastructure.

A non-invasive method that could accurately detect early stages of cancer and be routinely performed remains the “holy grail” for effective cancer management. The utility of such tests depends on their overall specificity and selectivity. Sensitivity is a measure of how well the method can accurately detect cancer (low false negatives) and is important to optimize to make sure that those who have cancer are not missed. An even more important metric for a cancer diagnostic is sensitivity, as it defines the rate at which the test incorrectly characterizes a sample as being positive for disease (false positives). Low sensitivity in a large screening population is particularly problematic as it results in costly, unnecessary, and invasive follow-up procedures.

“The liquid biopsy” or a simple blood test fits many of the criteria for cancer detection mentioned above. While blood tests for many types of cancer have been reported, prostate-specific antigen (PSA) is probably the test with which we have the most experience. Interestingly, the value of PSA testing for diagnosis of prostate cancer has recently been called into question, and there is currently a debate about how and when this test should be used. As an alternative to tests that detect a single cancer-associated biomarker such as PSA, there have been extensive efforts to leverage our ever-increasing knowledge of cancer-associated genetics to detect specific mutations that can be identified from circulating tumor cells (CTCs) or from circulating tumor DNA (ctDNA). Such tests are usually based on deep sequencing of blood-derived DNA with a focus on identification of specific predetermined mutations. While the Food and Drug Administration has approved a small number of liquid biopsy tests, they remain limited to confirm specific mutations in a known tumor cell type as a means to predict the response of a patient to a specific type of chemotherapy. Furthermore, most of the current reported studies using liquid biopsy to detect specific cancers involve a relatively small number of patients and even fewer healthy control samples, making accurate assessment of the overall specificity of the tests difficult.

A recent study reported last month by Cohen et al. addresses some of the most significant shortcomings of current liquid biopsy methods. Building from their earlier report demonstrating that enhanced sensitivity can be achieved by combining detection of cancer-specific DNA mutations and cancer-specific proteins, the authors developed a new type of blood test termed CancerSEEK. This test leverages a combination of information regarding the presence of established cancer-specific DNA mutations with levels of cancer-specific protein markers. By identifying an optimal set of small oligonucleotide segments (amplicons) that cover the regions surrounding multiple established DNA mutations found in diverse cancer types and a series of eight proteins that provide effective discrimination of these cancer types, it was possible to make a highly general blood test that had high sensitivity and selectivity across many cancer types. In addition, because the test makes use of the polymerase chain reaction to amplify the DNA regions containing the mutations and uses sample splitting to increase the ratio of mutants to nonmutant sequences in each reaction, the test could be used to detect the tiny amounts of mutant DNA that exist even in the early stages of cancer. The CancerSEEK test was validated using blood samples from 1005 cancer patients who had nonmetastatic but clinically detected cancers of the ovary, liver, stomach, pancreas, esophagus, colorectum, lung, and breast. The inclusion of 812 normal healthy donors allowed accurate determination of the overall sensitivity and specificity of the method. While the sensitivity ranged from 69 to 98%, depending on the cancer type, the specificity was >99%, with only 7 of the 812 healthy controls being scored as positive. The authors suggest that CancerSEEK could be performed at a cost of less than $500,
thus making it a viable approach for routine (i.e., annual) testing to catch cancers before it is too late to effectively treat them.

In addition, because CancerSEEK makes use of a combination of DNA and protein markers that are tumor type-specific, the results from the screening also provide valuable information regarding the affected organ system. Therefore, once a sample is flagged as positive, the test data can be used to focus efforts to localize and then remove the lesions. This ability to make an early diagnosis of a primary solid tumor and its potential location perfectly synergizes with recent advances in high-contrast imaging methods, potentially allowing surgeons to focus on early stage small lesions and achieve high cure rates with limited morbidity. Collaboration of biologists, biochemists, and chemists to develop more effective and specific contrast agents is necessary to reduce false positives that are likely to result from highly sensitive imaging methods that are used on small, early stage tumors. Luckily, a number of new classes of molecularly targeted imaging agents are currently making their way through clinical trials, so the future looks bright for the early detection, confirmation, and treatment of many of the most common types of cancer.

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Notes
The authors declare no competing financial interest.

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