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A prescription for cancer diagnostics

Cancer research has made great strides in identifying effective therapies for treating advanced-stage tumors. The next challenge is moving the battle to earlier stages of disease.

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The genomic variation underpinning common advanced cancers has come to light thanks to sequencing efforts by international scientific alliances such as the Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC), as well as by individual academic research centers (*Nat. Med.* **23**, 703–713, 2017). These types of scientific investigation have also revealed the tremendous molecular diversity of late-stage tumors, and have accelerated the development of targeted therapies to treat patients according to the genetic and epigenetic profiles of their cancers. Despite these advances in precision medicine, there is no conclusive evidence to date that molecularly targeted drugs can efficiently improve the survival of patients with advanced tumors (*Lancet Oncol.* **16**, 1324–1234, 2015). History has taught us that the earlier a tumor is diagnosed and treated, the greater the chances are that it can be eradicated. So one of our best chances to reduce cancer mortality today is to identify and treat tumors when they are more localized and less genetically diverse, and, therefore, more curable.

Screening protocols for early detection initiated in the past few decades, such as testing women for human papillomavirus (HPV) infection—which can cause cervical cancer—or regular high-resolution imaging to detect breast and lung cancers in individuals at risk, have made a substantial impact in reducing cancer mortality (*N. Engl. J. Med.* **357**, 1589–1597, 2007; *N. Engl. J. Med.* **365**, 395–409, 2011). However, some of these approaches are hindered by a lack of specificity and are prone to subjective interpretations that often lead to overdiagnosis and unnecessary treatment.

The need to detect and treat tumors at earlier stages was a central theme at the April 2017 annual meeting of the American Association for Cancer Research (AACR) in Washington, DC. To achieve this aim, we need more reliable biomarkers that can accurately detect the presence of a malignant neoplasm to form the basis of cost-effective screening tools. Screening programs based on these biomarkers must be made accessible to relevant population groups, and the impact of such long-term programs on mortality rates must be rigorously evaluated and optimized.

A powerful technology that holds the potential for early cancer diagnosis—as well as for monitoring tumor burden and evolution or spotting minimal residual disease after treatment—is the detection of cancer-specific mutations in blood-based tests that analyze circulating tumor DNA (ctDNA). These so-called liquid biopsies have been shown to have reasonable predictive value for measuring tumor burden in small cohorts of individuals with early- and advanced-stage cancer, and the technique received approval from the US Food and Drug Administration (FDA) in 2013 and the European Medicines Agency (EMA) in 2015 for the assessment of specific epidermal growth factor receptor (EGFR) mutations in lung tumors in the absence of tumor tissue biopsies. The challenge now facing these emerging diagnostic tools is to improve their sensitivity and specificity to detect tumor masses—particularly those that cannot be identified by tissue analysis or imaging procedures—and to differentiate life-threatening cancers in need of treatment from those that regress spontaneously or are indolent, and for which treatment could be detrimental to the patient.

And it will certainly be a challenge. Perhaps reflecting the scale of the challenge, two leading companies in the market of blood-based diagnostics just merged. Illumina's well-capitalized spinout Grail, now partnered with the Chinese firm Cirina, plans to conduct the type of long-term clinical trials of staggeringly high numbers of individuals—in the tens to hundreds of thousands—needed to validate a test that claims to be able to sort individuals into those with and without specific types of localized cancer before that cancer is diagnosed by existing methods. And these companies are not the only ones, or the first, to attempt to tackle the challenge of diagnosing cancer early on the basis of ctDNA analysis. South San Francisco–based Freenome was founded with the same goals in 2014. Whether ctDNA analysis will be sufficient to accurately diagnose patients with specific types of early localized cancer remains unclear. As discussed by Johns Hopkins University investigator Bert Vogelstein and others at the AACR meeting, integrating multiple types of molecular information, such as markers of DNA methylation, metabolites or microRNAs, from multiple sources, including organ-specific biofluids such as urine or cerebrospinal fluid, might be needed for an accurate biomarker.

What is clear is that these companies as well as academia-led efforts are attempting to tackle a problem that, if solved, would undoubtedly have an impact on millions of lives each year. The International Agency for Research on Cancer (IARC) estimates that the global incidence of cancer will rise to almost 24 million new cases by 2030. The ability to accurately diagnose cancer early, when it is localized and less genetically diverse, might spare patients from multiple rounds of ultimately ineffective yet toxic therapy. Considering the cost of the latest cancer therapies used to treat individuals with advanced-stage cancer, optimizing the efficacy of treatment will conceivably contribute to decreasing the cancer burden.

The study of advanced cancer has yielded an arsenal of knowledge and tools, including targeted therapies, sequencing technologies and processing of complex data. Bringing the full complement of this knowledge to bear on earlier phases of disease, through the development of biomarker-based tests that have been rigorously validated in defined patient groups, will bring the next revolution in oncology.