Editorial

The Cancer Genome and Diagnostic Blood Tests

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According to dogma in the information era of biomedicine, more DNA sequencing and protein profiling will inevitably lead to medical progress. An overview of the genetic landscapes of breast and colorectal cancers published online in Science on September 8, 2006 provides an opportunity to gauge how greater knowledge of the DNA sequences and the predicted transcriptomes of individual tumors may benefit efforts to prevent and cure cancer (1). Velculescu, Vogelstein, and colleagues at Johns Hopkins and other institutions sequenced 13,023 protein coding genes in the consensus coding sequence database in 11 breast and 11 colorectal cancers. Of the 13,023 genes evaluated, 1,149 were mutated, 242 were validated, and 191 were deemed candidate cancer genes (CAN genes). Usual suspects, such as APC, BRCA1, KRAS, and TP53, appear in the list but most of the CAN genes were not known previously to be genetically altered in tumors. Predicted products of the majority of CAN genes could be assigned to functional groups, such as cellular adhesion and motility and signal transduction, with mechanistic importance for carcinogenesis. How does a glimpse of the comparative genetic templates of breast and colorectal cancers through the prism of the consensus coding sequence database, itself a work in progress, alter our view of the cancer genome?

Apparentiy, the somatic mutational profiles of two common solid tumors are much richer and more diverse than suspected; an estimated 93 genes are mutated in a typical breast or colorectal cancer. Both the mutational spectra and the panels of CAN genes mutated in the two phenotypes show substantial differences. For example, metalloproteinase genes were mutated in a large fraction of colorectal but in only a small fraction of breast cancers. Mutations of genes regulating transcription were common in both but the specific genes affected varied according to tumor type. There was also considerable heterogeneity among the CAN genes mutated in tumors of the same tissue from different patients. The report by Velculescu, Vogelstein, and colleagues improves our view of the cancer genome. Does it advance the cause of reducing cancer morbidity and mortality?

The justification for information-driven biomedical research is the generation of useful hypotheses and in that regard the current report is unimpeachable. Information-driven research, however, is expensive and it is neither frivolous nor hopelessly Luddite to plead that dazzling genomic science should not disproportionately redirect funds away from more prosaic hypothesis-driven research, including outcomes research. An intellectually compelling, mechanistically based molecular test is useless unless cost effective and demonstrably superior to existing tests.

A case in point may be the detection in serum of mutant tumor DNA molecules from patients with colorectal tumors, which was pioneered by Diehl et al. (2). Accurate screening and diagnostic blood tests to select those individuals who really need an invasive investigation to confirm or exclude the diagnosis of a cancer are a worthy goal. The Vogelstein group asserts that “the evaluation of patient blood samples for mutant DNA molecules is a particularly attractive approach because such tests could detect many different forms of cancers.” They use BEAM technology (beads, emulsion, amplification, and magnetics; ref. 3) to amplify single molecules of DNA by the PCR. They were able to detect circulating mutant APC DNA from >60% (presumably symptomatic) patients with colorectal cancers that had not yet metastasized. However, in patients with even very large premalignant adenomas, no circulating mutant APC DNA could be detected.

For comparison, optical (4) and virtual colonoscopy (5) have >95% sensitivity for asymptomatic colorectal cancers and the current generation of fecal immunochemical tests has >60% sensitivity for asymptomatic, screen-detected colorectal cancers (6). When optimally done, optical (7) and noninvasive virtual colonoscopy (5) both have >90% sensitivity for asymptomatic large colorectal adenomas. It is inconceivable that a serum test for mutant DNA could supplant a diagnostic structural colorectal evaluation in already symptomatic patients, and a test that does not detect even large premalignant colorectal lesions is fatally inferior to existing methods for colorectal cancer screening. It might be argued that testing for circulating DNA from additional mutant genes to APC could improve sensitivity. However, from the Vogelstein group’s own evidence discussed above, the number and heterogeneity of genes mutated in each colorectal cancer are much greater than suspected previously. The challenge of assembling a suitable panel of probes for candidate mutant genes is therefore made correspondingly greater, and testing for multiple genes would not overcome the biological fact that mutant DNA from premalignant colorectal lesions seems not to reach the circulation. These problems would only be compounded by broadening evaluation of patient blood samples for mutant DNA molecules to screen detect multiple forms of cancer at the same time. If there are still many problems to be overcome before reliable cancer screening or diagnostic tests based on the detection of circulating tumor DNA are available, is proteomics closer to delivering the earnestly, if sometimes unrealistically, sought goal of a blood test for cancer?

The failure of later attempts to reproduce the near-perfect sensitivity and specificity of a proteomic approach for detecting ovarian cancer (8) has been widely discussed and sensible approaches to the evaluation of proteomic methods for cancer screening and diagnosis have been proposed (9, 10). Nonetheless, reputable journals continue to publish reports of proteomic analyses with unduly optimistic conclusions. One recent study cited the ability of proteomic profiling in a training set to distinguish patients who already had symptoms of colorectal cancer from healthy controls with 95% sensitivity and 91% specificity (11). Thus, proteomic specificity in a highly selected population was inferior to the specificity of guaiac-based or immunochemical fecal occult blood testing in an asymptomatic screened population (6, 12). If the mutational profiles of common tumors involve more
genes and greater heterogeneity than was thought (1), their transcriptomes are likely to be correspondingly more complex and proteome methods for their detection may have to cast a correspondingly broader net to have adequate sensitivity. In that case, optimization of sensitivity may seriously impair specificity.

As a generalization, which some will vigorously rebut, proponents of proteomics for diagnosing cancer place more emphasis on the exquisite sensitivity that is possible with the technology than on its specificity (13, 14). Experience from fecal DNA detection for colorectal cancer screening is instructive. Using an approach that identified abnormal DNA in stool, 52% sensitivity and 94% specificity were reported for detecting colorectal cancer in asymptomatic persons ages 50 years or older at average risk for the disease (15). In an accompanying editorial, Woolf pointed out that the prevalence of this ‘common’ cancer in the population screened is ≈ 240 cases per 100,000 (16); hence, colorectal cancer will be diagnosed in only 2% of subjects undergoing colonoscopy for a positive fecal DNA test. Under this scenario, the remaining 98% of those with a positive stool test might experience to place an ethical obligation first to review possible outcomes: for example, the degree of reassurance that is appropriate if the test is positive, and the example, the degree of reassurance that is appropriate if the test is negative, what to do if the test is positive, and the implications of a negative diagnostic work-up after a positive blood test. The average primary care physician-patient encounter lasts 16 to 19 minutes (19, 20) and the agenda for this brief encounter is already almost impossibly full. The American College of Physicians even suggested recently that primary care, the bedrock of the U.S. health care system, is at grave risk of collapse (21).

Vogelstein and the Johns Hopkins group have published another landmark report (1). Prospects for the development of tests with sufficient sensitivity to detect minute quantities of circulating tumor products are dazzling. Well-tried and more pedestrian techniques will be required for their evaluation. Clearly, we have much work to do before any blood tests for the diagnosis of cancer in asymptomatic patients based on tumor DNA or protein sequences are ready for the clinic, let alone the primary care clinic.

**References**

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