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## Early Detection: The Real Way to Beat Cancer

*Harry Glorikian* Several New Biomarkers May Be the Key to Catching Cancer Early

More than 40 years after President Nixon declared the War on Cancer in 1971, we are losing that battle. According to the American Cancer Society 1.67 million new cancer cases will be diagnosed in the U.S. in 2014. About 586,000 Americans and six million people worldwide will die of cancer in 2014.

Despite massive investments in treatment and prevention, cancer mortality among people under 85 in the U.S. has fallen a meager 8% since 1975. This has led many to wonder if our current strategy makes sense. As Einstein once said, insanity is doing the same thing over and over again and expecting different results. Will the “cure” for cancer come from more blockbuster drugs, or is the answer much simpler and now within our grasp?

Spending on cancer therapeutics is massive, with worldwide sales of \$85 billion in 2013,<sup>1</sup> and multiple drugs with \$100,000 plus price tags on the market. However, on average, only a quarter of patients respond to any particular treatment—that’s a dismal response rate, and few of those are actual cures.<sup>2</sup> This feverish focus on cures has dominated the research since President Nixon declared war on the disease in 1971. But the results are disheartening at best.

### Cancer Mortality Rate

As shown in *Figure 1*, this approach has yielded meager results; as mentioned earlier, the overall cancer mortality rate in the U.S. for ages younger than 85 years has fallen by a meager 8% since 1975. Heart disease deaths by comparison have dropped a whopping 60% or so—many times more than cancer deaths.

As shown in *Figure 2*, the survival rate for many cancers is similar. The trick is actually to find the disease early. Find it early, and the odds of survival approach 90% with most patients receiving just low-risk surgeries. But find the cancer late, in stage III or IV, and the only resort is treatment with toxic therapeutics and blasts of brutal radiation. Survival rates also drop precipitously. So it is very important to combat cancer with early detection and targeted cures based on active pathway of the cancer.

We are so consumed by the quest to save the 586,000 Americans who will die from cancer that we overlook the staggering fact that more than one-third of all Americans, some 120 million people, will be diagnosed with

cancer sometime in their lives. Shouldn't we put as much energy into getting those 120 million people diagnosed early, as we put into curing as many as possible?

This is where several promising, novel biomarkers that are on the horizon come into play. We are at a crucial juncture where we can actually fish promising biomarkers out of the blood instead of relying so much on tumor biopsies. This is game changing and will have a profound effect on patients and the industry at large.

## Clinical Biomarkers

Some of these notable biomarkers are cell-free DNA (cfDNA), miRNAs, and exosomes. All of these can be sampled by noninvasive methods, and all demonstrate great promise as clinical biomarkers for cancer screening, prognosis, monitoring, and measuring a response to therapy.

Cancer cells naturally release cfDNA as they undergo apoptosis and necrosis. The abundance of circulating cfDNA in blood (up to 100 billion fragments of DNA per mL), along with a short half-life (16.3 min) and noninvasive nature of the testing make them well-suited for cancer detection: cfDNA serves as a liquid biopsy via a simple blood draw rather than invasive biopsies and it is a workaround for the problem of intratumor heterogeneity (instead of getting a slice of a certain part of the tumor, you get a wider range of cell sample). Analysis of cfDNA can detect genetic and epigenetic alterations that indicate the presence of cancer and its progression.

While cfDNA has been commercialized within the noninvasive prenatal testing (NIPT) market for a limited number of genes, research showing validity of measurement of cfDNA in cancer is still ongoing.

Recent research has shown that measurement of cfDNA has shown great correlation to tumor burden and that mutations were identified in more than 95% of tumors. cfDNA was detected in 100% of patients with stage II through stage IV NSCLC and in 50% of patients with stage I disease, and was shown to have 96% specificity for mutant allele fractions.<sup>5,6</sup>

## Circulating miRNA

In addition, detection of circulating miRNAs in serum and plasma has recently been shown to provide another promising type of noninvasive cancer biomarker. The remarkable stability of miRNAs makes them attractive for assessing disease characteristics in patients with metastatic disease that is difficult to biopsy.<sup>4</sup>

Exosomes are nanovesicles, secreted by most cell types, containing a molecular fingerprint of the releasing cell type and of its status. They are released in easily accessible body fluids such as blood and urine making them valuable noninvasive biomarkers.

A growing body of evidence suggests that exosomal DNA (exoDNA) represents the entire genome and reflects the mutational status of parental tumor cells highlighting the value of exoDNA in tumor-derived exosomes for early detection of cancer and metastasis.<sup>7</sup>

## Next-Generation Sequencing

These promising biomarkers need a technology that measures them in a sensitive and reliable manner.

Enter the one of the most promising technologies in molecular medicine—next-generation sequencing (NGS). NGS has rapidly evolved over the past decade and become more efficient. Its sensitivity, speed, scalability, and decreasing cost per sample make NGS a highly attractive technology. The growing body of evidence suggests that NGS is well suited to accurately measure these biomarkers using only a small amount of starting material and that it will generate results within a short period of time.<sup>5,6,7</sup>

As the analytical capabilities of NGS grow and cost goes down, it is poised to make the biggest near-term impact in clinical oncology. Interest is growing in applying NGS to measure these promising biomarkers for cancer diagnosis or disease and treatment monitoring.

It's important to note, however, that we are still in the early stages of figuring out how regulatory approval of clinical NGS tests will proceed. Assuming we cross that hurdle, we may have the chance to profoundly change how cancer is detected and how it is managed. The implications of this shift are a discussion for another article but needless to say it will cause a significant reorganization of industry and the medical establishment.

In conclusion, moving cancer from a death sentence to a relatively curable disease requires taking a new approach. Using NGS detection of cfDNA and other promising biomarkers offers the greatest hope in transforming cancer care. If we can accelerate this field, it may not be long before we gauge our progress in the war on cancer not by the large number who die, but by how few barely have to fight at all.

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<sup>1</sup> *Therapeutics Categories Outlook, Cowen and Company, March 2014*

<sup>2</sup> *The case for personalized medicine, PMC 3rd edition*

<sup>3</sup> "The Riddle of Early Detection!", Thomas Goetz 12.22.08 *Wired magazine*: 17.01

<sup>4</sup> Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer* 2011;11:426–437

<sup>5</sup> Sarah-Jane Dawson et al., *Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer, NEJM, Vol. 368, No. 12, March 2013*

<sup>6</sup> Newman AM, Bratman SV, To J, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nature Medicine*. 2014; published online 6 April 2014; doi: 10.1038/nm.3519

<sup>7</sup> Thakur BK, Zhang H, Becker A, Matei I, Huang Y, et al. (2014) Double-stranded DNA in exosomes: a novel biomarker in cancer detection. *Cell Res* 24: 766–769