Liquid Biopsies

Biotherapeutics (cell-based therapies, gene therapies, and regenerative medicines) have been dominating healthcare headlines recently…and with good reason. Three breakthrough treatments have already received FDA approval, a half dozen or so are predicted to be approved in 2018, and there's more than 140 in the clinical pipeline—all with life-saving capabilities.

Whereas biotherapeutics are the potential curatives for cancers and other diseases, liquid biopsies provide the insight into whether those diseases exist or not. What sets them apart from regular biopsies is: 1. They do so in a way that is non-invasive, or as minimally invasive as possible; and 2. They aim to identify diseases much sooner—certainly before symptoms appear.

Like a kid in his older brother's shadow, liquid biopsies trail behind. Still gawky and trying to find its own way, liquid biopsies hold as much promise as biotherapeutics though are, as of yet, immature and unproven. But, oh, the potential!

Liquid biopsy is the sampling and analysis of non-solid biological tissue, such as blood, urine, and cerebral spinal fluid (CSF), for detecting cancer as well as other diseases. Tissue biopsy is often painful and costly, not to mention risky for the patient. Because liquid biopsy removes the need for invasive surgeries and procedures those risks are mitigated.

"It is revolutionary," states Dr. Victor Velculescu, co-director of cancer biology and professor of oncology and pathology at the Johns Hopkins University Kimmel Cancer Center. "It allows us to think about using therapies that'll be more effective, because they'll be applied earlier on in the disease — with all sorts of improvements in the overall outcome, survival and morbidity or how patients do — just based on detecting the cancer earlier."[1]

The excitement over liquid biopsy certainly is not limited to physicians and their patients. The reason, as always, is money. In short, liquid biopsy is a market that's ready to explode to more than $20 billion a year. Market research has projected an overall compound annual growth rate (CAGR) between 20 and 25% during 2017–2023. The biggest disease indication segments are lung cancer, breast cancer, and colorectal cancer.

It is a veritable cash cow for multiple stakeholders along the healthcare spectrum. Major players besides the manufacturers in the so-called Global Liquid Biopsy Market: academic and research institutes, university laboratories, government and public health sectors, hospitals and diagnostic centers, and, of course, payers (insurers). Naturally, venture capital firms and other investors in the financial world have been eager to jump on this bandwagon, too. The formation of new companies and the acquisition of smaller companies already working in this field are rampant.

Results from multiple studies are turning up positive data in favor of the tests.

[1] https://www.cnbc.com/2016/01/11/a-revolutionary-blood-test-that-can-detect-cancer.html

Researchers at The Johns Hopkins Kimmel Cancer Center announced the development of three liquid biopsy, gene-based tests: CancerSEEK is a single blood test that screens for eight cancer types; UroSEEK, a urine analysis that indicates the presence of DNA associated with bladder cancer or upper tract urothelial cancer (UTUC); and PapSEEK, which uses cervical fluid samples to screen for endometrial and ovarian cancers.[2]

The New England Journal of Medicine published research out of Hong Kong in which a blood test could detect DNA associated with nasopharyngeal cancer.[3] Though the study was narrow—considered "the low-hanging fruit of liquid biopsies"—it did reconfirm that liquid biopsies could be effective and cost efficient.

Almost daily, internet site GenomeWeb reports on developments regarding companies' advancements in the field of liquid biopsy.

And, of course, there's COBAS (cobas EGFR Mutation Test v2). This was—on June 1, 2016—the first FDA-approved liquid biopsy. The COBAS test uses plasma specimens to identify patients with metastatic non-small cell lung cancer (NSCLC).

Time for a reality check.

It's probably unsurprising that over the past two years there have been many headlines pronouncing liquid biopsy as "the future of cancer detection." We've all been teased by its potential. Problem is, despite enormous progress, that's all we've really seen so far: potential.

Len Lichtenfeld, MD, deputy chief medical officer at the American Cancer Society: "We need to use our excitement about the work on liquid biopsies to make certain we can continue to advance this science. We definitely have come a long way, but we still have a long way to go."[4]

The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) came to the same conclusion in their latest findings. They reviewed data from January 2007 to March 2017 and found that circulating tumor DNA (ctDNA) assays—aka liquid biopsies—lacked clinical validity and utility. The researchers cautioned against rushing into clinical deployment of ctDNA since the technology is unproven. (Indeed, as of today the COBAS assay is the ***sole*** FDA approved liquid biopsy test.)

Notwithstanding the disappointing news, co-chair of the expert panel Alexander Lazar, MD, PhD. stated that "the ability to genotype tumors from blood samples is going to be transformational for oncology and pathology."[5]

Even when new liquid biopsies hit the market there'll still be unanswered questions that will impact the healthcare industry.

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[2] https://www.sciencedaily.com/releases/2018/03/180322103207.htm
[3] http://www.nejm.org/doi/full/10.1056/NEJMoa1701717
[4] https://www.cancer.org/latest-news/liquid-biopsies-past-present-future.html
[5] http://www.cancernetwork.com/cancer-and-genetics/caution-urged-when-using-liquid-biopsies-clinic

One of the most important factors to consider will be that of overtreatment. The best-case scenario of early detection is that a curative procedure can be administered. A surgery or drug or therapy will rid the disease from a person. An initial stage tumor is removed; the person is cured.

On the other hand, for many diseases the price to pay for early detection may be the potential for many more years of treatments. Let's say a disease is identified early on. Who knows if initiating treatments for a particular disease earlier would be more beneficial than getting similar treatments after detection later in life? For example, we now know that, overall, it makes no sense to check for prostate cancer in young men since about 99% of cases occur in those over the age of 50. So, if we knew a boy had a gene for prostate cancer would we do anything differently than we do already?

Continuing the prostate analogy, what if early identification meant that after years and years of treatment he'd eventually be cancer-free? Is enduring those decades of therapies any better compared to simple active surveillance? Or having the same treatment regimens albeit much later in life? (And this is to speak nothing of treatment mortality and morbidity.) In short, will up-front treatments be worth it in terms of efficacy?

Then there's the costs to be considered. The biotherapeutics we mentioned at the beginning of this article can and do save lives. But the price tags for such wonder drugs can cost hundreds of thousands of dollars each year. There's no guarantees that liquid biopsies will be any cheaper. Plus, getting more therapies much earlier on means increased healthcare costs. The cost-benefit ratio looms large even if such unproven technologies do come to fruition.

Cell- and gene-based therapies, regenerative medicines, and liquid biopsy treatments are the future of healthcare. It's the dawning of a new age. A new age filled with hope and unlimited potential. And maybe more questions than answers. For now.

But it's hard not to be awestricken about the possibility of detecting diseases—and thereby treating or eradicating them—before they even occur. Damn, if these aren't exciting times!