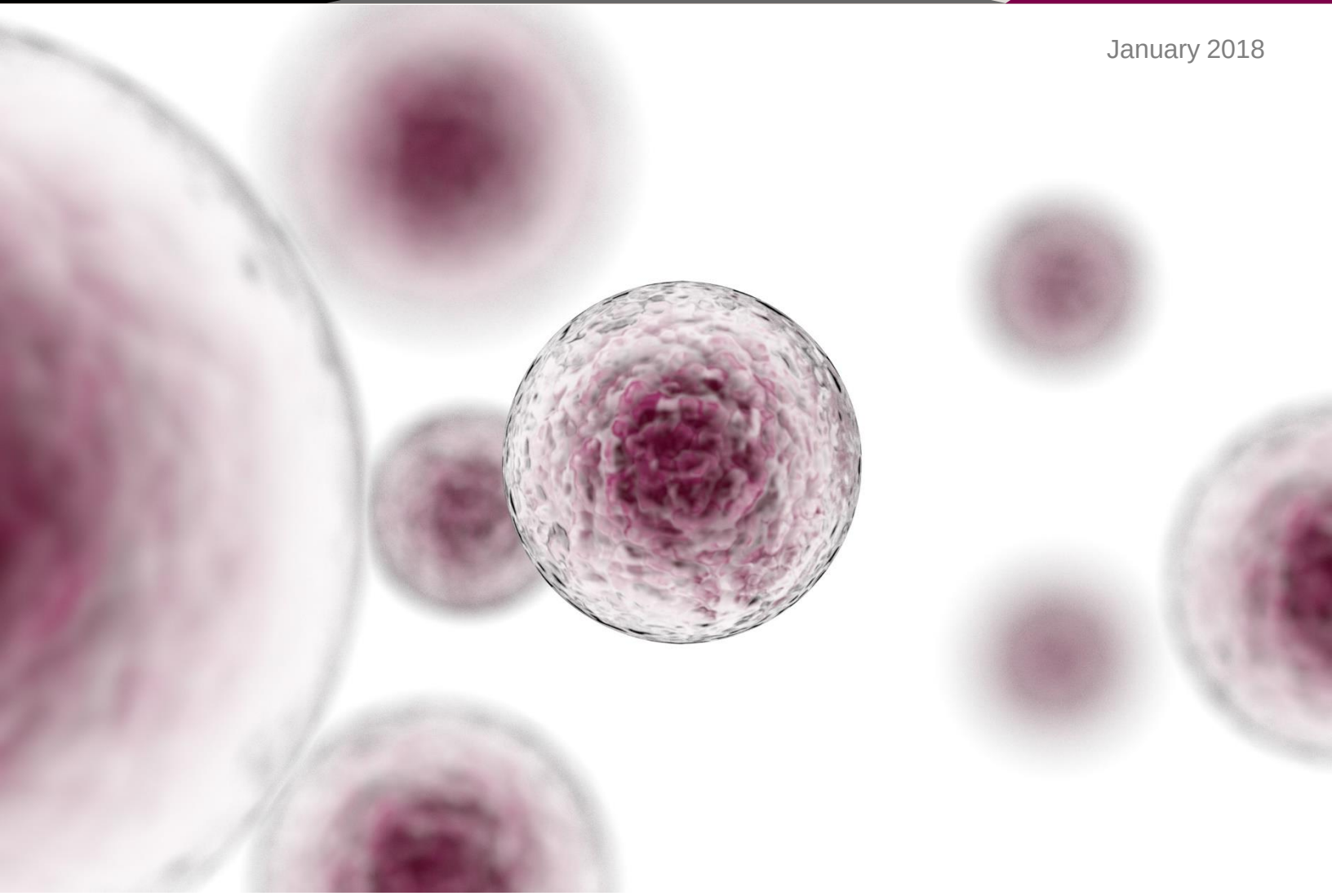
NAXION thinking

Viewpoint

January 2018



The Game-Changing Role of Biomarkers in Personalized Medicine

Lessons for Healthcare Innovators

By Debbie Kossman, Ph.D.

From a Game of Chance to a Game of Skill

One size has never fit all in oncology, but new discoveries about the biology of cancer, and about anti-tumor therapies that disrupt cancer, are making personalized treatment both a new paradigm and a new imperative.

The problem of selecting the best therapy for an individual patient has been most evident in oncology, where treatment regimens are often toxic and expensive, and may benefit only some patients. But the problem isn't limited to oncology. There are individual differences in responses to anticoagulants and antiretroviral therapies, to name a few. For that matter, some patients with certain diseases don't need to be treated at all, such as patients with low-risk subtypes of prostate cancer who are far more likely to die *with* their disease than *from* it.

Identifying in advance who will benefit from treatment has significant implications for the odds of success. Doing so avoids the "gainless pain" of toxicity, wasted time, and false hope. In other words, it reduces both the financial cost and the opportunity cost of ineffective treatment.

Obviously, diagnostic assessment isn't new – it's as old as medicine. What's new is testing that

gets us closer to the mechanisms underlying a drug's therapeutic benefit.

The first stunning success of diagnostics arrived with the launch of Genentech's Herceptin in 1998. Herceptin targets human epidermal growth factor receptor 2 (HER2) on the surface of tumor cells.

Herceptin's companion diagnostic, the DAKO HercepTest Kit, was used during Herceptin's clinical trials to identify patient candidates for therapy because only patients with tumors that overexpress the target protein benefit from Herceptin. Herceptin was the leader in changing the clinical trial paradigm to include prelaunch and pretreatment identification of likely patient responders.

The HercepTest Kit was the first FDA-approved "companion diagnostic": a test that is essential for the safe and effective use of a corresponding therapeutic product and whose use is mandated in the labels for both the therapeutic product and the diagnostic device. That paradigm shift involved several critical changes in thinking. It meant, first of all, that Herceptin was going to be used for only some patients, so the market would be smaller, but it also meant that this segment would be very well-served and could be treated with a high degree of conviction and optimism.

Powerful Implications for Clinical Management and *Marketing*

The concept of therapy must be redefined and broadened to include not just a specific drug but also a method by which we can screen and identify relevant patients.

While requiring Genentech to think more acutely about patient targets through the lens of clinical segmentation, it also meant a broader approach to professional marketing to include non-traditional stakeholders. In Herceptin's case, that meant surgeons and pathologists – surgeons, because of the importance of ensuring that they collect tumor tissue for analysis; and pathologists, because of their expertise about test quality and their role as gatekeepers in test method selection for clinical labs. The next generation of oncology drugs is being developed as targeted therapies that will work well in identified cancer cells that are genetically responsive to their mechanism. There are clearly implications for drug Innovations too. "Blockbusters" will be less common , of course, and the commercialization path will change by requiring simultaneous development and validation of a diagnostic assay with either in-house expertise or what can be complex negotiations with a partner diagnostics company.

Although both drug manufacturers and diagnostics companies share an interest in having a test used as much as possible, manufacturers resist deals that pay diagnostic developers royalties on eventual drug sales, preferring fixed milestone payments instead. And developers of diagnostics have little incentive to invest resources in tests that are relevant only to small numbers of potential patients.

Not Just for Oncology Anymore… But Also Not So Easy to Hit the Mark

Companion diagnostics have started to expand into areas other than oncology. Drugs for HIV, cystic fibrosis, and severe growth failure all now have companion diagnostics. But why have companion diagnostics historically been paired disproportionately with oncology drugs?

Diagnostic tests typically measure expression of a therapeutic target on or in tumor cells, or mutations in the gene of the therapeutic target, clearly linking the biomarker measured by the diagnostic test to the drug's therapeutic MOA.

In non-cancer indications, this is often either not clinically feasible or – given current technologies – impossible. For many neurologic, respiratory, ophthalmologic, or rheumatologic diseases, obtaining diseased tissue for testing is difficult, leading to greater reliance on less direct (and therefore less predictive) blood-based biomarkers, known as "liquid biopsies". And for many non-cancer conditions, we have not yet identified discrete, targetable, genetic underpinnings driving disease pathology.

Another challenge with many non-cancer diseases is commercial and ethical rather than scientific: the timing of the first clinical efficacy study. Outside of oncology, Phase I safety studies tend to be done with healthy volunteers who lack any abnormal tissue; investigational agents are not given to patients with non-cancer diseases until Phase II. As a result, for non-oncology drugs, there is considerably less time prior to launch in which to establish and clinically validate a diagnostic without delaying drug approval.

New Science Is Changing the Fortunes of Old Drugs

Although the first companion diagnostic was launched at the same time as its therapeutic partner (Herceptin), about 90% of all companion diagnostics available today were introduced sometime after their partner drugs became commercially available. While the percent of new pairings being launched simultaneously is increasing, established, commercially-available products are seeing changes in post-market labeling, including indications, as a result of newly-identified markers of product efficacy and safety. Again, Herceptin has been at the forefront.

The HercepTest Kit for Herceptin uses immunohistochemical testing (IHC) that yields scores of 0, 1+, 2+, and 3+, representing the degree of overexpression of the HER2 protein on the surface of tumor cells. At launch, Herceptin was indicated for patients with scores of 2+ or 3+. But a sizeable percent of patients with 2+ tumors do not respond well to Herceptin. A different testing method – fluorescence in situ hybridization (FISH) – measures the presence of her2 genes within tumor cells – rather than HER2 proteins on the surface of tumor cells, and is better able to distinguish Herceptin responders from non-responders among 2+ IHC patients. Although Genentech subsequently lost 2+ patients who are FISH- as Herceptin candidates, Genentech's clear guidance to oncologists to perform FISH testing on all IHC 2+ patients won the company respect for its commitment to the best diagnostic science.

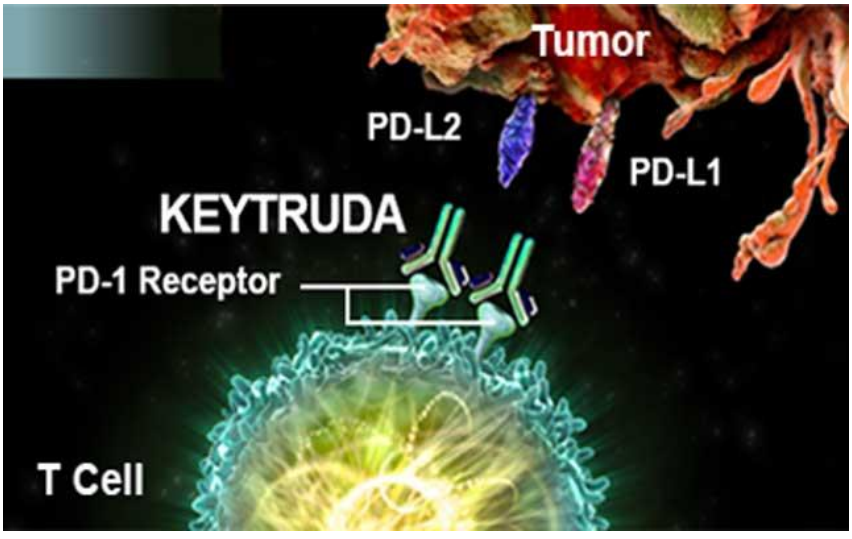
By contrast, the antiretroviral agent, Ziagen, was resurrected by new diagnostic knowledge. The nucleoside reverse transcriptase inhibitor was launched in 1998 but was soon discovered to cause life-threatening hypersensitivity reactions, leading physicians to abandon the drug, especially as new HIV therapies proliferated.

In 2008, 10 years after Ziagen's commercial introduction, the drug's label was revised to require patient screening for the HLA-B*5701 genetic variant. Patients carrying this allele are at higher risk of hypersensitivity, and Ziagen is now contraindicated for these patients. The ability to identify patients at lower risk has meant that Ziagen can once again be considered for some patients.

A Month of Biomarker Firsts

In May of 2017, the FDA approved the first companion diagnostic panel, ThermoFisher's Oncomine™ test. This molecular diagnostic panel can detect mutations in 23 genes implicated in non-small-cell lung cancer (NSCLC) using a single test from a single tissue sample. To date, the test serves as a companion diagnostic for four FDA-approved drugs for NSCLC, based on four of the biomarkers the test evaluates; Foundation Medicine is already working on another multi-biomarker, multi-drug companion test.

In the same month, the FDA approved the use of Merck's Keytruda for adult and pediatric unresectable or metastatic MSI-H or dMMR solid tumors, regardless of tumor site or histology. This shift in focus has enormous implications for the role of Keytruda and the clinical model for cancer therapies going forward.

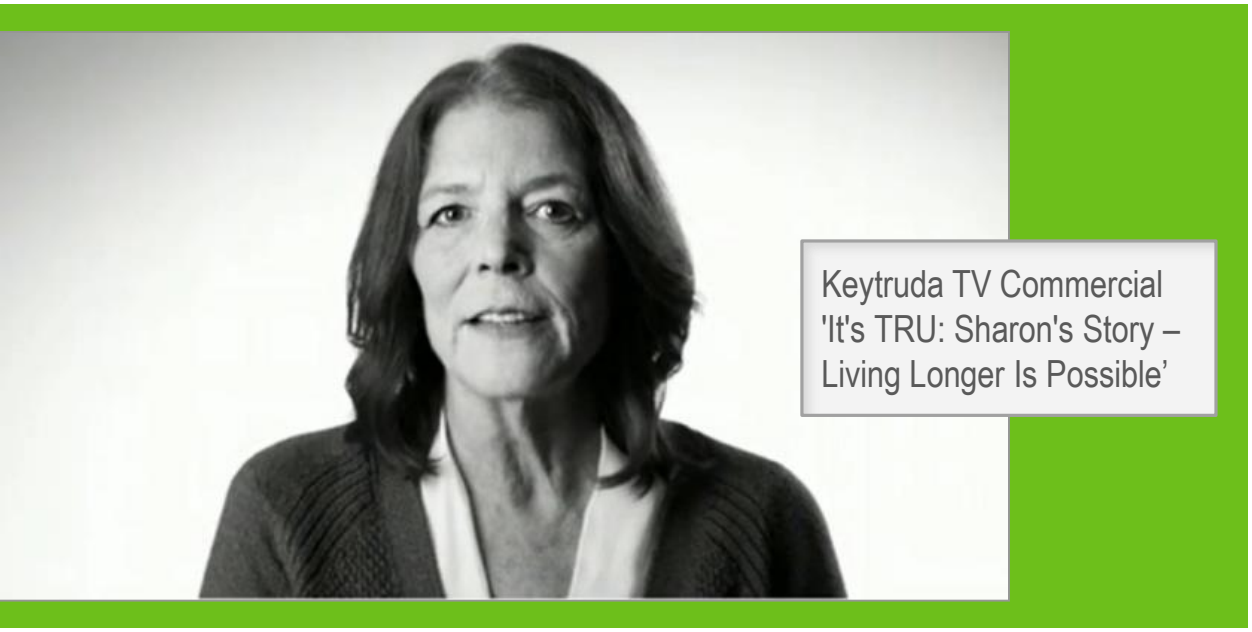


"… the first "biomarker (that) defines the indication." NEJM

Direct-to-Consumer Ads Building Bio-marker Awareness

Keytruda highlights the ascendance of biomarkers in another way. A series of television commercials for Keytruda's use in NSCLC has been running throughout 2017. The ads feature Sharon, a patient with NSCLC for whom "a biomarker test showed … high levels of PD-L1." Sharon goes on to explain that Keytruda can be used before chemotherapy for patients with high levels of PD-L1 whose tumors do not have an abnormal EGFR or ALK gene, as indicated by two additional biomarkers. The commercials reflect an emerging appreciation that the importance of biomarker awareness may fast be approaching the importance of product awareness among consumers.

In a rather stunning sign that diagnostics are advancing toward center stage and changing business models, Quest Diagnostics has been airing its own DTC television ads themed, "Good Health Starts with Knowing." These ads contain nothing about any disease or any therapy. Rather, they convey the messages that "knowing is the first step" and "knowing is everything." Whether there is ROI for Quest in these ads remains to be seen (their real strategy may be directed at sustaining market share in highly cost-competitive area of routine lab services). It's clear, though, that the growing role of diagnostics is not just redefining standards of care; it is also fundamentally changing the commercial model for our industry.



Diagnostic Tools Will Boost Margins *and* Advance Outcomes

The new mantra of value, defined in the broadest possible terms, places pressure on drug developers to change the traditional "numbers game" from population-level odds to high levels of certainty in smaller defined groups – the clinical equivalent of market segmentation. Higher certainty about treatment success delivers greater social value, and it also delivers greater shareholder value by commanding higher prices.

Implications for Drug Commercialization

It's never too early to search for predictive biomarkers.

The earlier you start, the better prepared you'll be to optimize patient selection early in clinical development.

Have a validated diagnostic tool before starting Phase III trials.

The ability to enroll the patients most likely to respond to your drug can reduce development costs by allowing smaller sample sizes, faster recruitment, and greater ability to detect statistically significant improvements in outcomes.

Take account of separate uptake curves for the diagnostic test and therapy in your launch planning and forecast projections.

A full prelaunch logistics plan is needed to ensure rapid availability and use of the diagnostic test to avoid a delay in uptake of your therapy. If asynchrony can't be avoided, your forecasts will need to reflect launch timing of both.

Educate all key stakeholders about optimal patient selection.

Physicians and patients both want to know what's best for individual patients; and payors require persuasive evidence not only that a new therapeutic agent deserves coverage but so, too, does pre-treatment diagnostic testing for likely responders.

About NAXION

NAXION is a broadly resourced, nimble boutique that relies on advanced research methods, data integration, and sector-focused experience to guide strategic, data-driven business decisions that shape the destiny of brands. Our specialized Healthcare & Life Sciences practice, the industry's oldest, is built on decades of experience and hundreds of engagements across the lifecycle from market entry to patient expiration. NAXION's NAscence Bio-innovation group, which provides specialized commercialization support to the Healthcare industry, has helped develop and launch some of the world's best-known therapies.

Our hybrid "enterprise DNA", which integrates authoritative research with consultative marketing application, is rooted in the firm's origins as the world's first business intelligence firm and subsequent decades as the National Analysts division of Booz•Allen. And our exceptional commitment to partnership reflects a unique, employee-owned organizational culture scaled to provide confident solutions to our clients' most challenging marketing problems.

About the Author

Debbie Kossman, is an SVP in NAXION's Healthcare practice, with over 30 years of experience leading engagements that have helped life science innovation companies commercialize groundbreaking therapies. Her cross-training in behavioral science and nursing gives her a unique patient-focused perspective that guides the creation of commercial and clinical value for drug marketers. In addition to a Ph.D. in Psychology from UPenn, she received a BSN from the Penn Nursing program and is training as an oncology palliative care nurse practitioner.

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