
# Economics for Diagnostics- Why Paying for Value is Necessary to Drive Market Success and Uptake.

Historically, diagnostic testing in healthcare has been bucketed as a commodity- cheap, frequent, and easy. This concept was born from run-of-the-mill testing: metabolic panels, blood cell counts, and vitamin D assays. These tests were produced (and priced) with the goal of being run at volume and lumped together on requisition sheets. Sometimes the tests were (are) so cheap and easy that overordering of tests for the sake of volume was easily overlooked, despite growing protests from payers about the value of those tests and whether their results were being used to inform patient management.

The issue of the price and volume of diagnostic testing is now complicated by the fact that there are really two categories of diagnostic tests: run-of-the-mill and esoteric. As compared with run-of-the-mill tests, esoteric testing is more complex, often involving multiple genes and/or algorithms which require a higher degree of clinical validation- such as Genomic Health's Oncotype Dx. A discussion that began with run-of-the-mill testing has bled into esoteric testing, with consequences for all stakeholders as commodity pricing and batch testing has made its way to sophisticated esoteric testing. This stifles innovation of the very testing that is the key to Precision Medicine, and prevents diagnostic technology from making an impact in healthcare.

The value of diagnostic tests should ultimately lie in their effect on patient outcomes, but their pricing rarely reflects that value. Tests can dramatically affect patient health by determining risk, changing treatment decisions, advising of adverse events, affecting time to treatment, and modifying patient perceptions and behavior. All elements of the patient management process must be considered when evaluating a diagnostic test, including incentives in our healthcare system which may run crosswise to the use of diagnostics. It may take years after a test is on the market to establish clinical utility and cost effectiveness, which is even more difficult to pin down in our fragmented healthcare system. Historically, commercial payers have reimbursed diagnostics as a percentage of the cost-plus rate Medicare sets – and re-evaluating those reimbursement rates is rarely done after coverage is established. Market economic value and clinical utility, and pricing for diagnostics is not revisited after coverage.

The fitness of a diagnostic test is a complex question that is generally evaluated using four criteria:

1) Reproducibility
2) Precision
3) Validity
4) Clinical utility

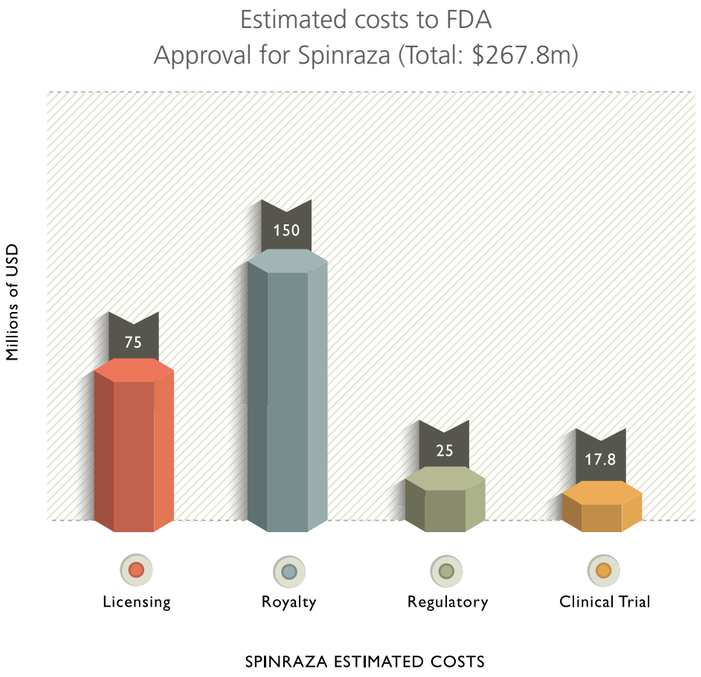
Reproducibility indicates reliability and is assessed by the variations between replicate measures, typically at different laboratories. The precision of a test demonstrates the consistency in test results while varying various parameters such as operator and instrument, and can be estimated by standard deviations/standard errors. Validity is defined as the ability of a test to accurately identify individuals harboring the phenotype or genotype in question, or not. Validity can be hard to quantify because it is often dependent on analytical and clinical sensitivity and specificity, and related to the chance of a true positive and true negative test result, respectively. The last parameter, clinical utility, is the usefulness of a test in a particular population and addresses how the test will change patient management and outcome.

The gold standard for clinical validation is randomized controlled trials (RCTs) which can measure how new tests impact clinical outcome and economics as compared to the current standard of care. RCTs are generally how new therapies are validated before they are granted FDA approval. First, new drugs must be proven safe (Phase I), then proven effective (Phase II), and finally proven superior to standard of care (Phase III).

If 'acceptable' response rates for drugs versus diagnostics are compared, real disparities are readily apparent. While diagnostics are held to sensitivity thresholds well over 90% and negative predictive values (NPV) 95%, drugs are regularly approved with response rates that hover around 30%, even less in terminal diseases like metastatic cancer or rare diseases where no effective therapy is currently approved. This means that statistically powering these trials is very different—a trial that needs to tease out the differences in thresholds confidently above 90% requires many more patients than one where the acceptable range is anywhere above 25%.

For example, in December 2016, the FDA approved Spinraza, made by Biogen, for patients with Spinal Muscular Atrophy (SMA), after a trial in only 170 patients[1]. The trial yielded results that Spinraza halted or slowed progression of disease in 40% of patients studied, a tremendous advance for this patient population. Despite being a targeted therapy, Spinraza was approved without the use of a biomarker or patient stratifying diagnostic to determine response. If a diagnostic company wanted to power a clinical trial to develop a test to determine response to Spinraza, a survey of clinicians found that the test would have to have an NPV of at least 95% in order for the test to be considered for use. The theoretical test developer would have to run a clinical trial of at least 550 patients to properly power the study to determine drug response at that confidence level[2].

But the real differences are most apparent in the market—Biogen priced Spinraza at $750,000 per patient for the first year, and $375,000 for subsequent years, which allows Biogen to quickly make up the clinical validation and clinical trial costs. A diagnostic company negotiating a price based on the current fee schedule would likely end up with a price point between $100 to $200 per individual test. If the trial cost $10 million to run, that means the company would have to run the test on 50,000 patients just to break even on the cost of the trial. (Figure 1)




*From Boston Business Journal, December 2016

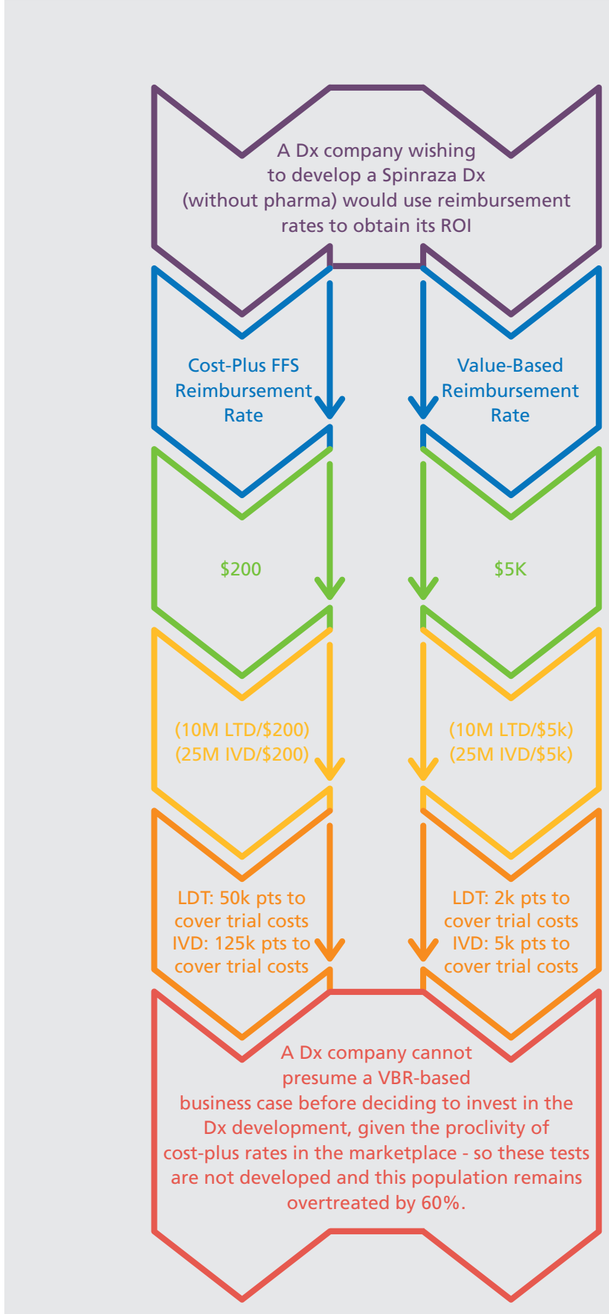
FIGURE 1. Costs for development of Spinraza and projected revenues: Included licensing and milestone payments to Ionis, as well as built in royalty payments, regulatory costs, and clinical trial costs, the estimated costs to Biogen for bringing Spinraza to the market at $267.8M[3], which doesn't include the Orphan Tax Drug Credit, making 50% of the trial costs exempt.



It is well established that clinical trials are the most expensive pre-commercial budget item for pharma, with some drugs requiring large, multi-hundred or even multi-thousand clinical subject trials that span years and run into hundreds of millions of dollars. The Tufts Center for Drug Development most recently estimated that the cost to develop a new drug has topped $2 billion[5], although those calculations have been disputed by some[4]. Factored into the budgets of the cost of developing a new drug that successfully garners regulatory approval are the costs of failure—of all the potential drugs that did not make it. Fortunately for pharma, they are able to capture those costs in drug pricing, and successful drugs more than make up for the clinical failures.

Clinical trials and validation are also the most expensive part of development for diagnostic companies and laboratories, but here it is difficult to see the ends justify the means. A properly powered clinical trial to validate a test for launch as a Lab Developed Test (LDT) can easily run over $10 million, while adding the required regulatory and manufacturing costs required to bring an In Vitro Diagnostic (IVD) to the market can surpass $25 million. This is where the math becomes challenging with commodity pricing for diagnostics. Making up the cost of the clinical validation and regulatory process can require selling more tests than the market actually carries for years to come. (Figure 2)

FIGURE 2. The challenges of recouping clinical trial costs: Using Spinraza as an example, a comparison of costs for a diagnostic company to develop a patient stratifying diagnostic test for response (or non-response) to Spinraza. This model assumes that the diagnostic developed would have to assume all costs for development, and compares the costs of an LDT test and an IVD test. The end calculation shows the total numbers of tests that would have to be run just to recoup the costs for running the clinical trial, which does not account for the assay development and technical validation, or costs of running the lab/company.



Overall, the diagnostics industry has been challenged to conduct health economic analyses to capture the value of the innovative technologies created. Pharma companies have set a precedent, during the clinical trials phase of development, to establish the clinical value and health economic benefits of the pharmaceutical product by communicating that value early and often to payers. When a diagnostic company takes a test to market, the company is either handed a categorical reimbursement price that is already established based on a cost-plus model, or, if the product is truly novel and innovative, the company can choose to wait until after product launch to make a case for value based pricing—which is never guaranteed.

This math illustrates why investors have been circumspect to invest heavily in diagnostic companies, and why the overwhelming majority of diagnostic companies and laboratories make the majority of revenue by something other than selling their own diagnostic tests—such as pharma services, clinical trials and contract development work. Pharma companies have been happy to underwrite companion diagnostic (CDx) development, including the clinical trials, since the concept was first considered with the advent of Gleevec and Herceptin. However, as previously discussed in this column, fee-for-service CDx deals don't allow the diagnostic companies to control the key levers of commercialization—pricing and reimbursement. Increasingly however, pharma companies are becoming savvy to the fact that if a diagnostic test required on the label of the drug is not successful, it will eventually impact drug sales and competition in the market. The old argument used to be that a higher priced diagnostic test would eat into the margins that the drug enjoyed by siphoning from the same bucket of money the payer uses to cover that patient population; the new paradigm is to realize that the success (or failure) of the diagnostic may be more directly linked to drug sales than previously believed.

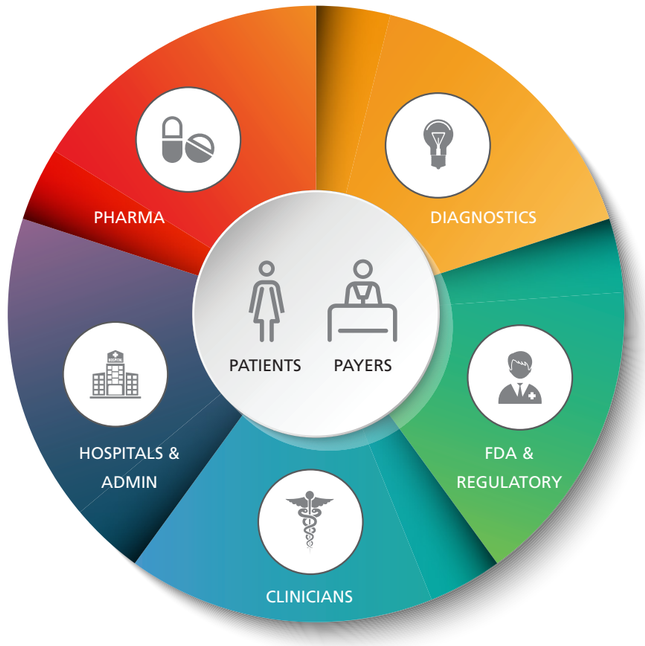



FIGURE 3. Our healthcare system is comprised of several interdependent stakeholders, including patients, clinicians, labs, hospitals, FDA, and payers. Both payers and patients are customers within the healthcare system.

We have to change our thinking. Previously, Precision Medicine has been characterized as a targeted therapy/companion diagnostic combination, giving little thought to the implications of pharma-sponsored economics for these diagnostics. But in this 'post-companion' era, Precision Medicine requires a strong value-based argument for the diagnostics that will be directing these targeted therapies toward, or away from, patients. We must create an economic environment that makes it possible for diagnostics to enter the market with value propositions that include directing drugs away from patients due to mismatched genomic profile, adverse event likelihood, or known drug-drug interactions. Today, inherited cost-plus economics are keeping valuable diagnostics locked out of our healthcare system.

A new paradigm must be created: one that allows another financial party besides pharma to fund diagnostic innovation through value-based payments. Value-based payment, in which the reimbursement of the diagnostic is commensurate with the savings exhibited by the healthcare system that uses it, has been a much-debated concept in healthcare to date. Like the discussion around patient-centered outcomes, its existence is accepted but its application is unclear. A clear model for value-based payment must begin with the party that determines the value of the diagnostic in the first place: the payer. Historically, the payer has been the last stakeholder in the healthcare workflow to be introduced to a diagnostic, because the journey of the diagnostic from patient to lab ends with a claim being filed for reimbursement to the payer. In this new paradigm however, the payer must be among the first stakeholders to be engaged. (Figure 3)

While some physicians are adopting the principles of value-based healthcare, most are still compensated on a fee-for-service model. Cost-plus reimbursement rates for diagnostics translate into lower (or no) reimbursement for the physicians, as compared to the established procedures physicians trained for years to perfect and the drugs they are used to administering- and are well compensated for.

As with every business case, the value of any product in any market is what the customer is willing to pay. Payers have been resistant to paying high amounts for diagnostic tests, because the value hasn't always been clear, and because diagnostic companies have always made their argument too close to, or after, commercialization. But payers are also shouldering the economic consequences that come with a lack of robust diagnostic technology in their members' care. They continue to pay for ineffective therapies and unnecessary biopsies, because the value conversations around better diagnostics are in their infancy. What's more, payers are recognizing this – that they have a role to play in bringing diagnostic technology to bear on patient care and financial toxicity.

The model of the future is bringing two new partners together: payers and the diagnostics industry. When we consider that patient care is also member satisfaction, and that lower costs of care mean decreased premiums, co-pays, and financial toxicity for patients, with improved patient outcomes as a bonus, we come to a revolutionary concept. Diagnostics are the arena where the interests of patients and payers align—and developing diagnostics with payers involved early in the process directs the economics in the interest of both customers.

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