Mission possible

MOVING DIAGNOSTICS TO THE FOREFRONT OF PRECISION MEDICINE

by Hannah Mamuszka

Why diagnostic companies need to control their own market.

It has been nearly 20 year since what most consider to be the advent of Precision Medicine, when two targeted therapies (Herceptin and Gleevec) were first approved to treat narrowly defined groups of patients based on specific mutations in their disease. At that moment, diagnostics, which had previously been seen as valuable, but not always critical information in medical decision making, rose in their importance. Unfortunately, in the intervening 20 years, far less progress has been made in the use of diagnostics than would have been expected back in 1998. Across all disease areas, most physicians continue to practice trial-and-error medicine, despite more and more data being available to guide treatment decisions.

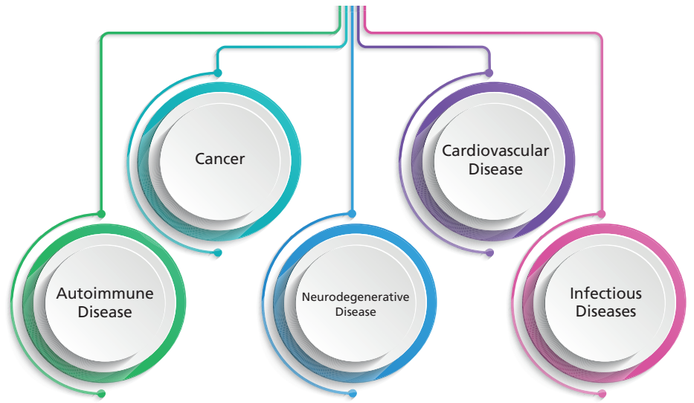
The Institute for Systems Biology describes "P4 Medicine" as the Precision Medicine goal of the future: Predictive, Preventive, Personalized, and Participatory[1]. The real value in the concept is to get an understanding of both host and disease at the molecular level with the goal of preventing disease before it causes systemic damage; to determine patient response to potential therapies, as well as adverse events, and to determine risk, of both action and inaction. Since more than 93% of people have genetic variations that cause them to respond differently than the 'average' population to specific drugs, understanding those variations, and their presence within individual patients is essential to Precision Medicine. It requires participation by the patient, as well as the physician, in the use of data to determine the best course of treatment. And the key to obtaining this information is diagnostics. Diagnostics are essential to the implementation of Precision Medicine across healthcare- to determine disease risk, likelihood of response, pre-determine adverse events, and detect recurrence.

But even if we agree that diagnostics are essential to the future of Precision Medicine, today's reality is that they are unequal participants in our healthcare system. While AdvaMedDx famously cited that, "the use of diagnostics guides upwards of 70% of

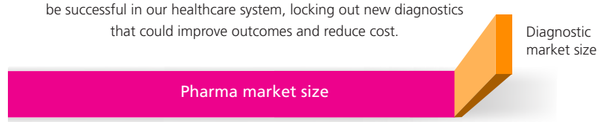
Figure 1 The Value of Diagnostics

Technology in diagnostics should be at the forefront of medical decision making, to inform on disease risk, drug response, adverse events, disease recurrence.

Studies have shown that diagnostics inform at least **70%** of clinical decision making, but only garner **2%** of the economics in our healthcare system.



These type of economics make it challenging for new technology to be successful in our healthcare system, locking out new diagnostics that could improve outcomes and reduce cost.



Pharma market is 100x of the MDx market, but diagnostics are the best way to control drug costs by determining responders, adverse events, and outcomes. However, those ratios make it challenging for diagnostics to impact the market.

treatment decisions while only taking in 2% of healthcare spend"[2], those statistics only described the beginning of the problem.

The crux of the issue is ROI. Because diagnostic companies frequently cannot determine or guarantee reimbursement ahead of market launch, they are attracted to the non-dilutive cash deals that pharma offers for Companion Diagnostic (CDx) development. This is especially true for VC-backed earlier-stage diagnostic companies who are desperate to find an earlier return on their investment than they can in the high-risk direct clinical market. When the first companion diagnostic tests were developed- bcr/abl and Her2, it seemed clear that diagnostics would be leading partners with pharma in Precision Medicine. The Gleevec story was magical- a drug designed so specifically as to only target a particular mutation in a particular cancer (later slightly expanded), and a test for that mutation, Bcr/Abl, was already available for use in both diagnosis and prognosis, readily available. Similarly, with Her2 and Herceptin, patients who were diagnosed with breast cancer were already being tested for Her2, which prior to the development of Herceptin implied a much poorer prognosis. Knowledge of these markers and identification of these patients seemed critical, obvious, necessary. Diagnostic companies realized that the targeted agents that pharma was developing in oncology would need tools to find these patients, and eagerly looked to partner with pharma companies to reap a portion of that value.

But the open dirty secret is this: Companion diagnostic deals are generally bad deals for diagnostics companies. While diagnostic companies have tried to stake claim to a small percentage of the drug royalties obtained by the pharma company, pharma prefers to pay on a fee-for-service model. The diagnostic companies don't own the clinical data, or the rights to the test development (because pharma is paying, it's a pharma product). They can't control pricing, and can't control the market because the IP laws don't allow them any protection from me-too competing labs[5]. This is not a successful business partnership model, because one side has all the power. Economic models of CDx deals have found that the value of the test is only 2-4% of the corresponding drug[3]. This level of economics does not allow the CDx developer any opportunity to fully penetrate the market, educate clinicians on the benefits of using the test, or recoup any investment ahead of competition.

While few diagnostic executives will discuss this publicly, most of them are forced to do deals with pharma- they need the non-dilutive cash that the relationship brings, but struggle with the post-deal market economics for the actual diagnostic test. At the Personalized Medicine Coalition annual meeting, held in Boston in November, 2016 Brad Gray, the CEO of Nanostring suggested that his company has little choice but to pivot their business model to work with pharma, because it is the only way that they can guarantee to get paid. This should not be so -diagnostic companies need to be able to control their own markets, without dependence on pharma.

The Complementary Diagnostic[4] provision is terrible for diagnostic companies, although becoming more popular with pharma companies because it relaxes restrictions even further. The essence of the complementary provision is that a clinician could test a patient using a 'Complementary Dx', but then treat the patient empirically, regardless of the result of the test- meaning that the physician could treat the patient with a therapy that the test indicated against. What this signals to physicians and payers is that the test is not valuable. With both clinicians and payers, what is most frequently heard is: the results of the test need to change the way the patient is treated. This new rule implies directly the opposite, and represents a very dangerous path for diagnostics. It is extremely difficult to argue for the value if a test, if it is not directly impacting care. Outside of oncology, the FDA generally approves targeted therapies without any tools for patient stratification, despite low response rates. Figure 2 (can we adapt this figure? From Nature)

In major disease areas like autoimmune disease, there are no diagnostics associated with drugs that treat some major diseases, despite the fact that drugs for Rheumatoid Arthritis or Multiple Sclerosis have response rates between 30-40%. That means that for a drug like Humira, a therapy targeting the TNFα pathway approved across 12 indications which grossed $16B in 2016, approximately $10.4B of the drug costs went to non-responding patients. And that doesn't include the cost of side effects and adverse events.

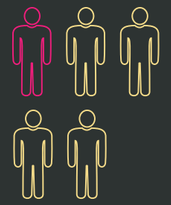
In most diseases today, patients are treated empirically. They are given a drug for their illness and told to wait a while, sometimes 6 months or more, to see if they respond. If they don't respond, they are moved on to the next therapy. This trial-and-error approach to patient care is the opposite of Precision Medicine, and wastes massive amounts of time, money and resources. Progressive diseases worsen while the patient is experimenting with a line of therapies, often experiencing adverse events that require hospitalization and/or additional therapies. All of these drugs are targeted therapies, but no one is forcing pharma to find the target patients.

Forcing pharma to find the target patients. How can this paradigm change? One way is post-approval Companion Diagnostics, where diagnostic companies are responsible for the design and implementation of the entire process from assay development through market access, allowing diagnostic companies to control the assay design, endpoints, study powering, market and theoretically, reimbursement. This allows the diagnostic companies to focus on developing tests not to gate in the

IMPRECISION MEDICINE

For every person they do help (red), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (cream).

1. ABILIFY (aripoprazole)
Schizophrenia

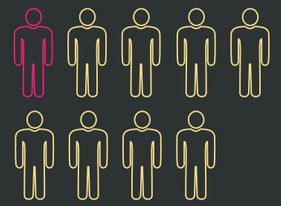


2. HEXIUM (esomeprzole)
Heartburn

3. HUMIRA (adalimumab)
Arthritis

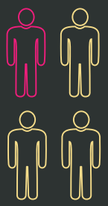
4. CRESTOR (rosuvastatin)
High Cholesterol

5. CYMBALTA (duloxetine)
Depression



6. ADVAIR DISKUS (fluticasone propionate)
Asthma

7. ENBREL (etanercept)
Psoriasis



8. REMICADE (infliximab)
Crohn's disease

9. COPAXONE (glatiramer acetate)
Multiple sclerosis

10. NEULASTA (pegfilgrastim)
Neutropenia

FIGURE 2. Nature, 2015 Schork, N. Personalized medicine: Time for one-person trials.

Drug	Disease Area	2016 Sales	Percent Responders	Cost of non-response, in Drug Cost only (waste)
Humira	Autoimmune	$16.1B	25%	$12.075B
Enbrel	Autoimmune	$8.87B	25%	$6.66B
Remicade	Autoimmune	$7.83B	25%	$5.76B
Abilify	Anti-psychotic	$6.5B	20%	$5.2B
Neulasta	Infection	$4.7B	7%	$4.37B
Advair	Asthma	$4.3B	5%	$4.9B

Figure 3. All drugs are targeted therapies, not just in oncology. The cost of not finding patients with those targets significantly drives up the overall cost of healthcare.

highest number of patients, but to develop diagnostics that address the largest and most relevant clinical questions in medicine today.

In order for diagnostic companies to be successful in this model they need to understand that they serve two classes of customers simultaneously: customers who provide them with clinical requirements, such as physicians and patients, and customers who provide them with financial requirements, such as risk-bearing physician groups, and payers. Diagnostic companies must become comfortable with the concept that until both customer classes are satisfied, the ROI (in the form of reimbursement) will not be forthcoming. No matter how technically advanced the technology is, the value is in the application, and the role that application plays in the care continuum. So how do we go about maximizing the certainly of diagnostic ROI?

Diagnostic developers need to cooperatively determine what constitutes clinical utility, what appropriate risk thresholds are, and what the necessary endpoints are for development to be successful in the market. Diagnostic companies must also be able to have proactive discussions in the market about reimbursement, and that reimbursement must be commensurate with the value that the diagnostic provides to the market. In order to impact patient care and ultimately reduce cost, diagnostic companies must have a clearer path for successin the market, where they can count on the parameters for success. As one pharmacy director for a large national health plan put it, referring to diagnostics, "Healthcare is confounding. In no other industry can the customer not give the supplier their vendor requirements."

The lack of transparency and value for diagnostics in healthcare has led to a downward cycle of value, which makes investment challenging and market success increasingly unlikely. The lack of communication of those vendor requirements has a significant trickle down effect in healthcare. Today diagnostic companies develop tests based on their scientists, lab and clinical observations, feedback from key opinion leaders (KOLs) and academic societies. They validate these tests, mostly under the CLIA model, because going through the FDA process for a diagnostic test tacks on many additional years, and somewhere around $24M in additional regulatory and development costs, both which are nearly impossible for all but the largest labs to recoup. When the are ready they launch onto the market and lobby (beg) to be paid, armed with their own data and the support of their KOLs. Unfortunately, the KOLs aren't the actual financial customers of the tests. That role goes to the payers, both commercial and government (Medicare and Medicaid).

Because there are no guidelines for obtaining guaranteed reimbursement successfully, and even fewer for obtaining true value based reimbursement, (value here being defined as a derivative of the value that the test brings to the market), commercialization often stalls. Payers argue, often rightfully, that the tests are not sufficiently validated, that they present too much risk, that the clinical studies were not powered appropriately or performed objectively, and request additional data before agreeing to coverage.

Investors look at the commercial situation for diagnostics and see no clear path to return on investment, because there is no clear way to determine what a test will be worth, determine the barriers to getting on the market, and forecasting revenues. Historically, while waiting for a CPT code, diagnostic companies have been expected to float on the market without payment for 18-24 months. Compared with pharma, diagnostics are at a substantial disadvantage in almost every way- regulations, market access, and ultimately reimbursement.

At industry conferences, reimbursement speakers will frequently discuss how the goal for diagnostics is commodity pricing, that however the test can be run the cheapest should be the goal. While that may be a valid argument for routine clinical chemistry and pathology, for complex risk assessment, patient stratification, prediction of adverse events, determination of response, detection of disease recurrence, etc., it is absolutely not. Commodity pricing doesnot allow for innovation to succeed in the market, let alone appropriate clinical validation, powering of clinical trials, assessment of heterogeneity in the patient population, or other critical building blocks of robust diagnostics. So how do we connect the need for robust diagnostics in Precision Medicine to the financial customers who can reward the industry for these dramatic improvements in cost and outcomes of care? As the old saying goes, necessity is the mother of invention.

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