Mission Possible

MOVING DIAGNOSTICS TO THE FOREFRONT OF PRECISION MEDICINE

by Hannah Mamuszka

Beyond the Economics

In a sense, when we have been talking about the goal of Precision Medicine, we have been discussing the value of diagnostics, with little to show for more than a decade of conversations. In the same way that nurses experience 'alert fatigue' with the advent of electronic notification systems, where the frequency of alarms causes them to become easily ignored, the healthcare industry may feel some fatigue at the prospect of yet another discussion on 'value'. Just as unsettling in today's healthcare environment, is the concept that value has different meanings depending on the stakeholder. According to Robert C Pendleton's review of the ongoing University of Utah Health's 'The State of Value in U.S. Healthcare' survey, patients and physicians fundamentally disagree on the definition of value. When patients selected the five most important value characteristics, 90% of patients chose combinations different from ANY combination chosen by physicians. But as conflict creates opportunity, our national game of value telephone may be spurring a re-evaluation of the value of diagnostics in healthcare.

In my last column, I wrote about the need to reconsider economics for diagnostics in order to create a viable commercial path for diagnostics to succeed, and to drive towards improved outcomes, better economics, and the goal of Precision Medicine. Diagnostics are the tools that not only diagnose disease, but also stage it, assess its aggressiveness, determine disease phenotype and genotype, quantify risk of adverse events, and assist in therapy and intervention selection. In the United States, high prices for drugs and procedures are readily tolerated, if not accepted, as a sign of their value and a reality in healthcare, even if those drugs and procedures don't deliver an improvement in symptoms or an increase in lifespan. Diagnostics, which may determine likelihood of success of those drugs or procedures, are considered secondary in importance. We readily accept (whether we realize it or not) drugs with response rates of 20-30% or less, (ex: Humira in ulcerative colitis, Avastin in breast cancer) and procedures with failure rates of 30-50%, (ex: cardiac resynchronization therapy in heart failure), but our expectations of diagnostics require perfection, or they are considered useless or too risky to be used at all. This thinking has to fundamentally change for our healthcare system to improve care.

Economics aside, there are many arguments to be made for better utilization of diagnostics across disease management. With limited exceptions, our current model in healthcare is largely 'try-and-see'- start a patient on a therapy or perform a procedure without knowing if they will benefit or have a severe adverse event. If the patient does well, then it worked; if the patient doesn't respond well, then it's on to the next therapy option.

The try and see approach is illogical, and possibly even unethical, when better options are now possible in 2018. Why do we continue viewing healthcare differently from the values that govern our other industries? Can you imagine if we maintained our cars how we treat patients? Consider the scenario of having car trouble, without utilizing automotive diagnostics. Your check engine light goes on, and you bring your car to the mechanic. Instead of running the now-standard computerized diagnostic to determine the problem that caused the check engine light to go on, the mechanic tells you that 20% of the time that light goes on, it's the carburetor, so he'll fix that. If the light comes back on, come back and he'll change your oil. If that doesn't solve the problem, come back and he'll try a new spark plug. And so on. In 2018, if your mechanic was treating your car like this, you would find another mechanic who ran diagnostics immediately- no one would tolerate a try-and-see approach with their cars; it's far too expensive and wastes too much money and time. Why don't we have the same standards in healthcare?

Technology exists, now, at scale and a price that enables the rapid development, deployment, and improvement of diagnostics to stratify for risk, response, and adverse even determination across disease areas. This wasn't true twenty or even ten years ago, but it is now. PCR machines are available in virtually every clinical lab; sequencing costs have dropped faster than Moore's law would have predicted; bioinformatic tools allow for the interpretation and correlation of complex data; tools and kits for sample processing and handling have streamlined sample collection, processing, and shipping, and electronic health records are making data more and more accessible and shareable every day.

There are many consequences to trial-and-error medicine beyond just the economics, though the monetary costs are very real and have broad impact on how healthcare is delivered. The cost alone of continuing to

administer costly drugs and therapies to patients without stratification is in the billions annually in direct cost of ineffective treatments alone. Employers would also cite lost productivity due to ineffective therapy as a direct cost. And adverse events and side effects alone cost the US healthcare system $30 Billion a year[1].

Within oncology, perhaps nowhere is there a more critical need for assessment of response and adverse event determination than in immuno-oncology, where diagnostic tools lag far behind the drug approvals and therapy combinations can exceed $400k. Despite the perception generated by marketing hype, the reality is that far fewer patients have a durable response, and a high percentage of patients have significant enough adverse events to lead to between 30-40% discontinuing therapy[2]. These adverse events range from the relatively manageable inflammation of the lungs, pancreas, bowel, and liver, potentially leading to pneumonitis, colitis, pancreatitis, diabetes, and liver damage. Endocrine effects such as irregular levels of thyroid, adrenal, and/or pituitary hormones have been observed, and in these patients, up to half will require hormone replacement for life despite early steroid therapy. Less frequently, severe and potentially fatal side effects can occur, including immune-mediated myocarditis.

The lack of robust diagnostic tools for immunotherapy (IO) was recently the subject of a discussion at the Molecular TriCon meeting in San Francisco, where the fact that for IO, receiving accelerated approval has meant approval in defined populations-—either in second-line applications, or with the use of less than ideal biomarkers like PD-L1, which is a poor surrogate for response. The meetings attendees' discussion acknowledged that because of pharma sponsored co-development, pursuing the best precision medicine strategy doesn't always match up with pursuing commercial success. The result? Accelerated approval for drugs with paired inferior biomarkers, so that when superior tests become available, such as the Nanostring signature or tests that analyze tumor mutational burden (TMB), it is very difficult to overcome both the regulatory hurdles and market perception that a new biomarker that is not on the label of the drug could be superior in determining response. The practical result of this is that too many patients are tested with PD-1/PD-L1, not enough patients are tested by the with the next generation tests that better predict response, fewer patients respond, and more patients are subject to serious adverse events without any therapeutic benefit. How could we facilitate developing high value diagnostics for IO? In the case of PD-1/PD-L1, development began with the pharmaceutical company as the customer. But it is the payer who pays for this diagnostic, and the subsequent drug, and the patient who must bear the treatment the diagnostic points to. Where were they, during the cycle of development of PD-1/PD-L1?

Consider the clinical path of patients diagnosed with Neurofibromatosis type 1 (NF1). NF1 is an autosomal dominant condition caused by mutation/deletion of the NF1 gene. With a birth incidence of 1 in 1,900–3,000, NF1 affects 100,000 Americans each year. The link between malignancy and NF1 is well established. 30%–50% of patients with NF1 have plexiform neurofibromas, benign tumors with the potential to become malignant (malignant peripheral nerve sheath tumors, MPNSTs). Patients with NF1 are also at higher risk of developing intracranial, gastrointestinal, breast tumors as well as other soft tissue cancers. The overall risk of developing all cancers has been noted to be 2.7 times higher (4.02 in young women under 50) in people diagnosed with NF1 than in the general population, and the cumulative risk of any cancer noted as 59.6% in NF1 cases compared to 30.8% in the general population (Finnish Cancer Register).

Despite the knowledge of increased risk of cancer, very little proactive screening is performed. Whole body FDG-PET and whole body MRI (WBMRI) are imaging techniques used when existing plexiform are suspected to be malignant: i.e. rapid growth, pain, numbness, costing $4,900-$6,700/scan. A simple blood test using DNA and epigenetic markets of malignant transformation in NF-1 patients could assess the lifetime risk of benign tumor transforming into cancerous ones, triage patients direct to surgical removal, and save money prioritizing when WBMRI and FDG-PET scans are needed and detect cancer earlier, when it is easier (and cheaper) to treat. Early removal of NF-1 related tumors cost an average of $14k, but late removal and treatment costs an average of $96k/year and up to $200k/year[3]. Alas, at this time, despite the knowledge of the markers within the clinical community and the costs of the current paradigm within the payer community, no such diagnostic exists.

Many diseases are progressive-patients progressively get worse and deteriorate to the point where when a patient finally gets on a satisfactory drug regimen, their quality of life has permanently declined. Take the diagnostic odyssey that is Multiple Sclerosis (MS) as an example, which is heterogenous in severity, rate of progression, and response phenotype to therapy. There are more than 159 different genetic variants of MS, four common sub-types (Relapsing-Remitting, Seconding Progressive, Primary Progression, and Progressive-Relapsing); more than fifteen approved therapies with response rates that average around 32%, and more than sixty drugs that treat symptoms and adverse events. Despite the spectrum of the disease, there are no tools for patient stratification of response to therapy, no tools to assess likelihood of flares or to prevent them, which means physicians prescribe therapy after therapy, the majority of which are ineffective, waiting to see which one has an impact on the patient's symptoms.

The landscape for the management of MS has changed dramatically since Disease-Modifying Therapies (DMTs) were introduced, but the costs of these agents remain a subject of much discussion. Even with the emergence of newer DMTs for patients with relapsing forms of MS, costs for all DMTs approved by the FDA have increased markedly. The average annual DMT cost per patient with MS in the United States in 2004 was $16,050, comprising approximately half of all direct medical costs for patients with the disease; the current average annual cost for the agent interferon (IFN) beta-1b was greater than $60,000[4]. Overall, the costs of DMTs in the US have increased annually at rates 5 to 7 times higher than overall prescription drug inflation, and substantially above rates for other drugs in similar biologic classes[5].

These costs substantially impact patients with MS in several ways, both in the overall cost and how their disease is treated and managed. Health insurance companies have developed tiered formularies, which have nothing to do with likelihood of response for a particular patient. Frequently, payers require step-therapy trials of DMTs for patients, and because there are no stratification tools to distinguish patients, many of the current agents are considered therapeutically equivalent by Payer Pharmacy and therapeutics committees, so the formulary status of an individual agent may be determined by pricing contracts. What if we had tools to help steer payers and physicians towards the drugs most likely to work so that they could be used first-line, earlier in the disease progression to slow it down, and that could make it into the formulary decision? While drug formularies are incredibly complex, they do not take into account the fact that the drugs they gate are all targeted therapies, and do not have an equal chance of working on each patient. What if we had tools to help physicians avoid putting patients on therapies that didn't impact the disease at all, or helped avoid serious side effects? How much would that improve quality of life, the ability to continue work (and play) for patients with Multiple Sclerosis?

An additional layer of complexity is that indirect costs associated with MS can also be substantial, including difficulty continuing to work. A study by Kobelt et al found that among patients with MS taking DMTs, 41% were working, with only 63% of these patients working full time. More than 40% took early retirement because of their MS, with 25% who stopped working despite having early retirement benefits of pension[6]. Because of the difficulty in disease symptom management, MS patients also have substantially increased use of sick leave associated with disease relapse, much higher than rates of patients without the disease. It has been reported that employees with MS have more than six times the number of sick days compared with healthy employees, while the annual costs for disability were nine times higher for employees with MS, while indirect costs, including the loss of earnings due to the use of unpaid leave, were more than four times higher for the MS cohort versus employees without MS[7].

We have come to accept trial-and-error in medicine and in healthcare, despite the growing evidence that we could do better using diagnostic technology. While Precision Medicine is most advanced in the high stakes field of oncology, diagnostics could and should be implemented in disease areas where patients are not at such high immediate risk, and where there are a myriad of treatment options but no clear path to successful disease management. Doing this will enable our healthcare system to take the time necessary to determine the specific areas of diagnostic need in complex and chronic disease. U.S. healthcare spending on diabetes is over $100B – how could diagnostics guide the patient journey in multi-layered areas?

Payers and patients have often found themselves on opposite sides of the healthcare debate, but in the view of diagnostics – unnecessarily so. Payers and patients are interested in answers to the same questions – will this treatment work, what is the risk, and how much will it cost. In this era of increasing financial responsibility on the part of the patient, the cost question is of high priority to both parties. Diagnostics can greatly assist in navigating a value discussion between payers and patients. What forces are needed to develop diagnostics that allow patients to feel comfortable with treatment decisions and that care isn't being unfairly rationed and that allows payers to assess both risk and true cost-benefit? And if those diagnostics could be developed, how would they be rewarded, in the new currency of value? In 2018, diagnostics could significantly improve care, but we have become accustomed to trial and error medicine. What forces need to be applied in healthcare to change this expectation, improve patient experience, and have the added benefit of reducing cost?

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