

Mission Possible

MOVING DIAGNOSTICS TO THE FOREFRONT
OF PRECISION MEDICINE

by Hannah Mamuszka

A DIAGNOSTIC VISION FOR PRECISION

The Journal of Precision Medicine was founded in order to bridge the gap between the evolving technology in healthcare and the clinical needs of patients. The tools that bridge that gap are diagnostics – diagnostics, and the data they generate, have the power to make medicine more precise and individualized for all patients. Diagnostics today can be defined as all the tools we use to make better decisions in healthcare - including imaging, pathology, molecular and proteomic methods, and the bioinformatics we use to interpret them.

We are in an amazing time in healthcare technology- we have abundant platforms that can run simple and highly complex assays to determine risk, warn of adverse events and toxicities, distinguish between responders and non-responders to determine who should get which therapies, and a growing list of exciting applications. We can port huge amounts of data up to the cloud and sort it, use complex bioinformatics to analyze it, and encrypt it (and argue about who owns it all day long).

Precision Medicine depends on diagnostics. Risk assessment for disease is very precise- patients who are BRCA1/2 positive have a

55-65% chance of developing breast cancer as compared to 12% of the rest of the population, and a greater than 50% chance of developing ovarian cancer, contrasted with a 1.3% chance in the overall population¹. Precisely knowing that a patient has either mutation informs their life decisions and allows for long term disease mitigation strategies, if desired.

Knowledge of adverse events using metabolomics and pharmacogenomics to assess gene-drug and drug-drug interactions is remarkably precise, with studies showing that prior assessment before treatment, especially in polypharmacy patients, can dramatically

reduce readmissions, ER visits, and mortality rates, resulting in significant per patient savings. There are almost a million serious adverse events annually in the United States, and over 140 medications have pharmacogenetic considerations in their label, but testing for these is inconsistent at best and most frequently absent².

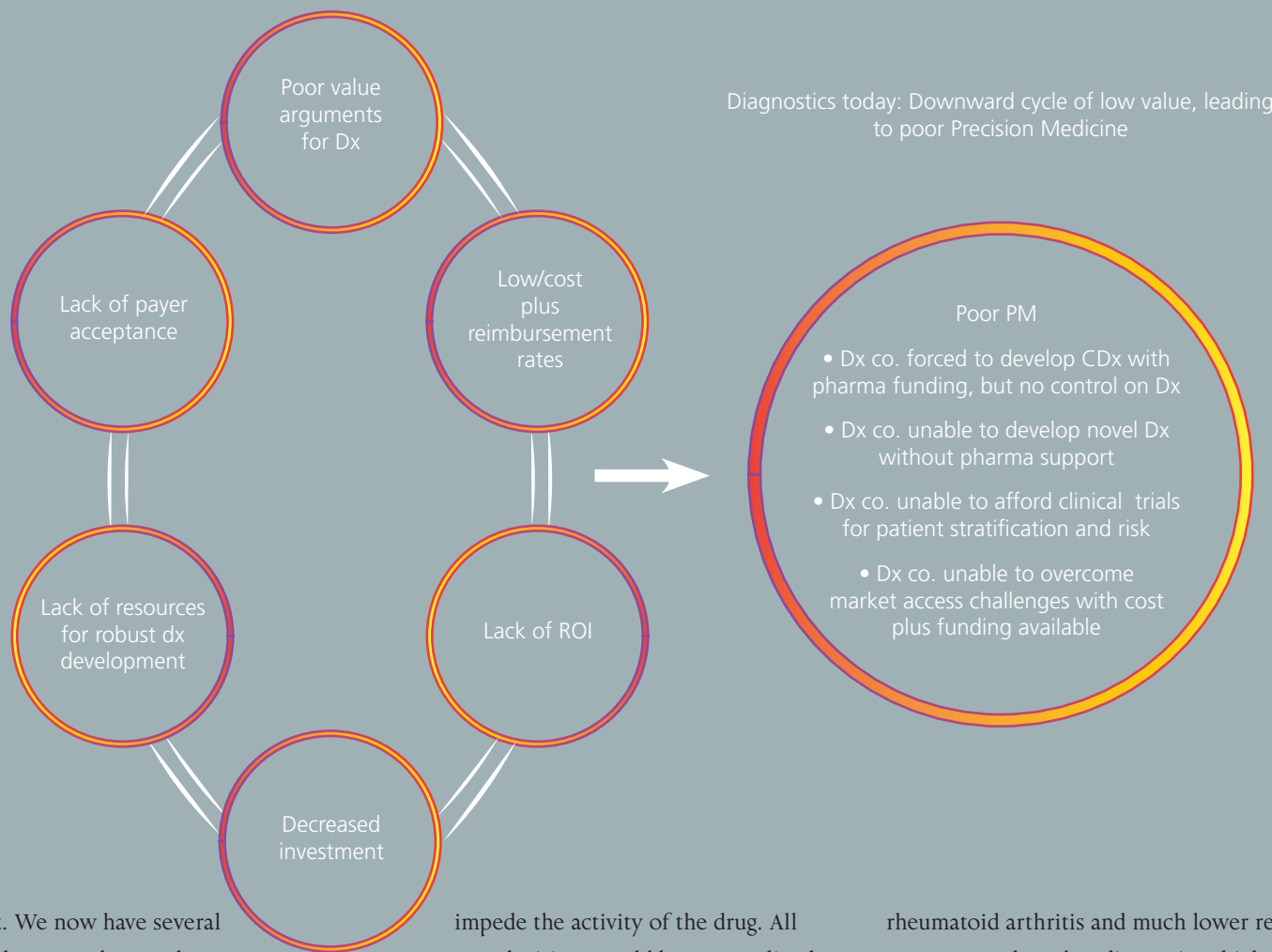
The most 'famous' examples of Precision Medicine are in oncology, where the early success stories of HER2 detection for Herceptin and Bcr/Abl detection for Gleevec demonstrated significant clinical value in matching a mutation with a drug designed specifically to

Diagnostics (Dx):
The Keys to Precision Medicine (PM)

"21st century medicine promises to delivery the right treatment, to the right patient, at the right time..."

Robust Diagnostics

- Quantify risk of disease
 - Diagnose disease
- Determine Rx response
- Identify adverse events
- Identify genetic phenotypes



bind to it. We now have several additional approved examples, including drugs targeting EGFR, ALK, ROS, and others- although the response rates hover around 30-40%, even with the target present. Clearly, there is work to be done.

Depending on where you live, where you are treated or what you're working on, you're probably exposed to a tiny bit of Precision Medicine. Maybe your doctor suggested you get BRCA tested because breast cancer runs in your family, or during a recent pregnancy you were offered Non-Invasive Prenatal Testing (NIPT) to screen for genetic abnormalities. While this is Precision Medicine at work, optimal use of diagnostics and technology in healthcare is hardly standard of care.

The power of Precision Medicine really comes into focus when you consider the fact that all drugs are targeted therapies, meaning that all drugs tend to only work in a particular patient population where the patients have the drug target present, and nothing to biologically

impede the activity of the drug. All treatment decisions could be personalized to a patient's genomic, genetic, metabolic/ pharmacogenomic phenotypes. Such a shift would reduce cost from both overtreatment with ineffective therapies, and adverse events. Economic data shows us our healthcare is overburdened by paying for drugs that don't benefit patients. Drug response rates across all diseases are poor, although these sobering statistics are often masked by marketing stories of success in a small portion of patients.

Oncology is frequently the focus with response rates hovering around 20% despite costs soaring to over \$250k per year, but a 2015 study in Nature reported that the top ten highest-grossing drugs in the United States help between 1 in 4 and 1 in 25 of the people who take them, and for some drugs, such as statins to lower cholesterol — as few as 1 in 50 may benefit³. Humira®(adalimumab), an anti-TNF alpha inhibitor, is one of the largest grossing drugs in the world (\$16B+ in 2016) with a ~35% response rate (at ACR₅₀) in

rheumatoid arthritis and much lower response rates across the other disease in which it is approved- including ulcerative colitis and Crohn's Disease⁴. Our healthcare system is overburdened by paying for drugs that don't benefit patients, but it does not use diagnostics to reduce that cost.

Diagnostics can dramatically reduce the cost of ineffective therapies – but our healthcare system doesn't pay for this true Precision technology. While most of the focus around Precision Medicine is in oncology, consider codeine, a common painkiller no one would consider precise. But the amount of CYP2D6 enzyme, which breaks the drug down and makes it active, varies dramatically in people. About 10% of patients have very little of the enzyme, resulting in very little codeine being converted to morphine, and the patient remains in pain. For the 2% of people who have the opposite problem, the correct dosing of morphine by weight can get converted to morphine too fast, leading to a potentially fatal overdose⁵. By using an inexpensive diagnostic

tool, use of codeine could be far more precise. Surprisingly, this is almost never done – this type of testing is only routinely offered at ten hospitals in the country (as of 2016)⁵.

Why?

Medicine has been an art practiced by highly trained artisans; it is rapidly becoming a science needing highly skilled medical scientists. The overwhelming majority of physicians who are in practice today never had the opportunity to become educated on technology being used to develop diagnostics today - how digital PCR can determine genetic variation down to .01% sensitivity, or how next generation sequencing can enable enormous amounts of data to become digestible, so their limited acceptance of data generated by novel technologies is understandable. But diagnostics represent the technology that can enable physicians to better serve their patients. Physicians have been running ad hoc ‘N-of-One’ trials since time immemorial- starting a patient on a therapy based on the disease diagnosis and the physician’s own experience of how prior similar patients have responded, seeing how the patient does by monitoring their symptoms and asking questions, and changing the therapy based on the physician’s experience. We now have diagnostic tools which can provide data up front to eliminate at least some of the trial and error. How do we drive for broader acceptance? What is the true barrier here?

AdvaMedDx famously cited that diagnostics drive 70% of healthcare decisions (and could/should drive more), but only account for 2% of healthcare spend⁶. This translates to diagnostics being viewed as commodities: simple, cheap tests. This is a dangerous line of thinking – because it leads to low, ineffective reimbursement rates for diagnostics within the US healthcare system.

The Center of Medicare and Medicaid Services (CMS) sets annual payment rates for diagnostics based on a cost-plus system. These payment rates then trickle through to the commercial

insurers that reimburse the majority of Americans’ healthcare. Additionally, the American Medical Association (AMA) curates the code sets (CPT codes, in this case) that define diagnostics in the insurance claims management systems. Historically, in order to obtain a code for a diagnostic test, the test had to first be used in many labs – meaning, commercialized. In this way, diagnostics were being forced onto the market without any guarantee of their test being covered by an insurer – and if coverage was obtained, the payment rate would be a version of that same CMS cost-plus rate. This is all hardly a recipe for strong return on investment, which made it even harder for diagnostics to remove themselves from the “commodity” label. The vicious cycle that low investment and uncertain/low insurer coverage created has permeated the diagnostics industry, to developers large and small. Because of the lack of certainty around reimbursement, large diagnostic manufacturers have trouble investing in diagnostic development, as there is not always a path to recoup those funds. Similarly, small diagnostic labs are challenged to find investment, because venture investors can’t see a clear path to return. In both cases, this results in diagnostic tests being validated with smaller trials, that are not ideally powered, with often sub-optimal results. The historic requirement for lab usage prior to CPT code assignment facilitated a culture where diagnostics would be launched first and beg insurers for reimbursement (to recoup their commercialization costs) second. Diagnostic test developers never benefitted from a methodical, comprehensive commercialization approach – and thus never benefitted from feedback until their diagnostic was already created, and it was too late.

The economic problems for diagnostics in the time of Precision Medicine have been good for pharma. Because diagnostic companies barely make a margin on diagnostics, they welcome working with pharma on Companion Diagnostic deals, because pharma money is non-dilutive

and guaranteed. Because pharma is paying for the development of the diagnostic, they control the design and market to their advantage, with the goal of gating in as many patients in as possible, frequently resulting in suboptimal diagnostic tests (see: PD1 for IO, or the KRAS IVD for colon cancer).

Diagnostic companies are virtually unable to develop any tools for patient stratification without partnering with pharma because they cannot afford it, and pharma companies are only incentivized to develop companion tests if they believe their drug won’t pass through FDA without it. The complementary diagnostic provision, where the validated test associated with the drug can be run but the patient treated regardless of the test results, is particularly troubling for the diagnostics industry. It effectively tells physicians, payers, and patients that a diagnostic is optional to the ultimate treatment decision, which is exactly the opposite direction we need to go.

So, how do we change it?

Diagnostics belong in the very beginning of a treatment pathway, but financial incentives are aligned in the other direction. Can we redesign the system, and place Precision Medicine technology at the forefront of patient care, where it belongs? I think so.

References

1. J Natl Cancer Inst MS Bose et al (2002) 94 (18): 1365-1372; Cancer Risk Estimates for BRCA1 Mutation Carriers Identified in a Risk Evaluation Program.
2. PLOS One Elliott LS et al (2017) Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial.
3. Nature Schork, NJ (2015) Personalized medicine: Time for one-person trials.
4. Arthritis Research and Therapy. Rendas-Baum, R. et al. Ther. 2011;13(1) Evaluating the Efficacy of Sequential Biologic Therapies for Rheumatoid Arthritis Patients With an Inadequate Response to Tumor Necrosis Factor- α Inhibitors
5. Scientific American Maron, DF. (2016) A Very Personal Problem.
6. AdvaMedDx: A Policy Primer on Diagnostics (2011).
7. AMA CPT Code Application, Accessed March 22, 2017

Hannah Mamuszka is Founder and CEO at Alva10. Alva10 is focused on moving diagnostics to the forefront of Precision Medicine by executing a comprehensive strategy of value, economics, technology in diagnostic development and commercialization. www.alva10dx.com