ARE WE AT THE TIPPING POINT FOR PERSONALIZED MEDICINE IVDS?

by Mike Kolodziej and Louis Jacques, MD.

Medicine is full of examples of innovative and intuitively appealing ideas, some of which have really improved patients' lives and some that just turned out to be harmful, or at most marginal. In hindsight, for those flawed "good ideas" we can usually identify the faults in our reasoning, the facts we chose to ignore, fueled by an over exuberance of wishful thinking. Not infrequently, those good ideas have had significant support from important, powerful, and often very vocal individuals and institutions. And woe to those who express skepticism.

As physicians who have practiced during the infancy of precision medicine, and as payers who tried to assess the legitimacy of this "good idea", we have had a ring side seat to the frustration associated with the remarkably slow movement of precision medicine in vitro diagnostics (IVDs) from bench to bedside. Not that the technological advances have not been breathtaking. And goodness knows the excitement, enthusiasm, and hype have been overwhelming. But despite this, moving the promise to practice seems to have hit an impasse. Why? And how do we get the train back on track? Is this just a "good idea" or really transformative?

The truth is that in precision medicine we suffered from asynchrony. The science and technical capabilities of massive parallel sequencing moved really fast. The bio-informatic advances moved pretty fast too. But we failed to adequately consider the thing that is really important to doctors, patients, and payers; at the end of the day is the patient's health status meaningfully improved by the use of the test result to inform clinical care. Instead, we faced the old standbys of analytic validity and clinical validity; and attempts to establish clinical utility often stopped in mid journey with KOL attestations that they would use the test in their practices.

And so we find ourselves at this impasse, and a lot of animosity has been directed at payers because they wouldn't pay for the test or pay for the test-directed therapy. In fairness, the payers didn't really know if the test was any good; they didn't know how it was going to impact the care of patients; and they didn't know if the test-directed strategy was going to add benefit for the patient over the status quo. In today's value conscious environment, just knowing more just wasn't good enough. There was no universe where knowing the results of 400 gene sequences was going to impact the treatment a patient receives tomorrow, let alone whether it was going to be better than the one they received yesterday. Some pretty outrageous things have been said by people on both sides of this debate. Believe it or not, CMS has come to the rescue, and here is how.

As we write this, CMS is finalizing the proposed National Coverage Determination (NCD) on next generation sequencing (NGS) in oncology. While we can peruse the posted public comments and speculate on the outcome, there are three Medicare precedents that can inform our thinking about personalized medicine and diagnostic testing.

First, personalized medicine is not the sole province of genome based testing. Indeed, a thorough history can be sufficiently informative to guide patient care. In August 2009, CMS (the Centers for Medicare & Medicaid Services) published its NCD for Pharmacogenomic Testing for Warfarin Response. As they wrote at the time, FDA approved labeling for warfarin (Coumadin) indicated cautious initiation and titration, "The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes as well as for elderly and/or debilitated patients and patients with potential to exhibit greater than expected PT/INR responses to COUMADIN…" CMS recognized that cautious initiation and titration were already indicated in its core patient population (the elderly, permanently disabled, and those with end stage renal disease on dialysis) and that there was no available evidence of clear improvement to be gained from pharmacogenomic testing in Medicare beneficiaries.

CMS agreed to cover CYP2C9 and VKORC1 testing for warfarin response only under Coverage with Evidence Development (CED). Two clinical trials (GIFT NCT01006733 and WARFARIN NCT01305148) were approved in 2009 and 2010 respectively. The trials were designed to see if significant bleeding or thrombotic events would be significantly reduced by testing. According to ClinicalTrials.gov, GIFT completed in 2016 and WARFARIN suspended enrollment and the entry was last updated in 2015. We are not aware of any requests for CMS to reconsider the NCD based on these or other studies.

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Second, CMS has historically signaled a preference for coverage of IVDs that have successfully passed FDA review. In the 2001 negotiated final rule on Coverage and Administrative Policies for Clinical Diagnostic Laboratory Services, CMS wrote in a response to public comment, "…we will continue to consider FDA approval when appropriate in making coverage determinations on Medicare claims." (FR 66, November 23, 2001 58794).

This is also clearly stated in the NCDs on screening (HIV, Hepatitis B, Hepatitis C, colorectal cancer, cervical cancer, sexually transmitted infections). A typical example is the following, "CMS will cover screening for cervical cancer with the appropriate U.S. Food and Drug Administration (FDA) approved/cleared laboratory tests, used consistent with FDA approved labeling and in compliance with the Clinical Laboratory Improvement Act (CLIA) regulations."

Third, CMS and its regional contractors have recognized that evidence of clinical utility can be demonstrated directly or indirectly.

A direct method is illustrated in the warfarin studies cited earlier; a protocol that randomizes subjects to test guided or usual care, and that follows those subjects all the way to important health outcomes. An indirect method assembles an evidence based chain of logic, leveraging well accepted prior knowledge about patient care pathways and the effects of various therapeutic alternatives that might selected based on test results. This approach is easier when the therapies themselves have significant recognized harms such as neuropathy, significant anemia, surgical morbidity, etc. CMS illustrated this principle in the 2009 NCD on FDA-PET (positron emission tomography with fluorodeoxyglucose) in cervical cancer. "In addition, publications support the beneficial effect on initial treatment planning of cervical cancer (Chao 2008, Hillner 2008), with the majority of the effect being avoidance of futile surgery."

So where do the commercial payers stand? History has shown us that commercial insurers in the US almost always follow the lead of the world's largest insurer, Medicare. In cancer care this makes a lot of sense because there is so much more cancer in the Medicare aged population. This is probably going to be the case for precision medicine in oncology. We can draw a few conclusions already:

- Complex NGS tests require thorough review. Tumor genome profiling is not a CBC. While we don't want to chill innovation, quality assurance is necessary and FDA review should be the standard to strive for. Patients and doctors must be 100% confident in the results of NGS. There is little doubt some labs may not survive, but that may be the price for quality assurance.

- The evidence for clinical utility in NGS just isn't good enough for many clinical situations. A transparent, reliable and clinically relevant repository of mutations and outcomes is just what the doctor ordered. If you doubt the value of registries, take a look at how impactful the registry developed by the Cystic Fibrosis Foundation has been in that very rare and very deadly disease. One could argue that the real value of understanding the molecular biology of CF would not have been nearly as paradigm changing without the patient registry. Although CMS' coverage with evidence development (CED) was removed from the final NGS NCD labs should consider registries as a means to proving clinical utility and more. A goal of data sharing and democratization for the greater good will speed the adoption of personalized medicine.

- While there may be relevant concerns about the performance of some proprietary assays, in some clinical situations there just shouldn't be any debate about the value of the underlying paradigm. There is clear value of multi-analyte testing in NSCLC, and the reality is that often there isn't enough specimen for all the tests that need to be done unless you do NGS. It is time for payers to acknowledge this reality.

That said, the test developers need to be willing to contract around a competitive price. And if we can agree on some quality standard (as outlined in #1) there should be an opportunity for the free market to work.

- Time for pharma to shine. If payers are willing to pay for testing, this should trigger a tsunami in drug development. Every oncologist loves the idea of the NCI-MATCH trial. Now we can have a lot of biomarker driven match trials. These should accrue quickly because at the beginning, payers won't change coverage policy for therapeutics, so we will know about mutations but in the absence of these new trials we may not be able to do anything about them. This also may provide a great opportunity for RWE to come into its own, such that we can actually learn from every patient we take care of.

For the first time in a long time, there may be a path forward for precision medicine in oncology. Like most good compromises not everyone will be happy, but it would be a mistake to make the perfect the enemy of the good. We have the chance to move precision medicine from adolescence to productive adulthood.

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He is passionate about change and innovation, proven in his implementation of Coverage with Evidence Development (CED) under the Medicare program, co-creation of joint parallel review pilot between CMS and FDA, and his work to update Medicare coverage in FDA IDE trials.

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