

Personalized Medicine – Promise or Potential?

Remarks Delivered at the 14th Annual Personalized Medicine Conference

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Thank you, Paul, for that generous introduction.

Thanks to Ed Abrahams and the Personalized Medicine Coalition for inviting me to speak today at this impressive gathering. It's an honor to be here with so many thought leaders in healthcare and in personalized medicine.

It has been said that personalized medicine (PM) offers the promise of a future in which we can predict, prevent, and treat disease at the individual patient level in exciting new ways. It has also been said that the promise of precision medicine will lead to better clinical outcomes at a reduced cost.

BUT ... the dictionary tells us that a “promise” is “a declaration or assurance that one will do a particular thing or that a particular thing will happen.” I don't think PM is a promise, I think it is a field with some notable early successes and great potential. And like anything with potential, there are many opportunities and many obstacles to navigate. I'd like to spend some time talking about them today.

I've taken a bit of liberty with my topic today – I will go beyond the clinical laboratory industry and discuss:

- How is the role of diagnostics evolving within the world of personalized medicine?
- What are the challenges that we face, and do those challenges suggest that we are going to miss opportunities to advance personalized medicine?
- What do we need to do to move forward and make the promise of personalized medicine come to life?

We can find a paradigm for the opportunities and challenges of PM in a recent story from Kaiser Health News (KHN) entitled “Pricey Precision Medicine Often Financially Toxic For Cancer Patients,” about Kristen Kilmer, a 41-year-old woman from Spearfish, South Dakota. Ms. Kilmer was diagnosed three years ago with incurable breast cancer caused by a mutation in the PALB2 gene. The mutation was discovered by a next-generation sequencing test, which may cost up to \$6,000 and is often not covered by commercial insurance.

Ms. Kilmer has been successfully treated for three years with Lynparza®, which is an FDA-approved therapy — but only for breast cancer patients with a BRCA mutation. Her insurer declines to cover the drug, calling it experimental. The insurer says it makes coverage decisions based on “published, randomized data about the safety and efficacy of the requested drugs.” Ms. Kilmer is being treated with

Lynparza because she searched for experimental treatments, drives 12 hours round-trip to participate in a clinical trial and has spent much of the past three years “battling insurance officials and begging drug companies for financial assistance.” The manufacturer recently decided to stop providing her the drug without charge and the out-of-pocket cost to Ms. Kilmer would be \$17,000 per month — on top of the approximately \$81,000 her family has already spent out-of-pocket treating her cancer. She decided to discontinue treatment because she did not want to burden her family with the cost. “Within hours” of the article running in KHN and USA Today, the manufacturer called to inform Ms. Kilmer that it would continue to provide financial aid to support her taking the drug.

Really I could just stop here because this story so perfectly frames the issues and opportunities of PM, but Ed would probably not be happy to have 35 minutes to spend up here making shadow bunnies. So, let’s examine this in a bit more detail.

The story starts with a diagnosis of breast cancer and a sequencing test to try to identify the mutation. Here Ms. Kilmer was fortunate: someone involved in her treatment knew to order this kind of test. This should not be assumed: one major obstacle to PM and targeted therapies is lack of physician awareness of companion diagnostics and therapy options. Broadly speaking, there is still insufficient emphasis in physician education on the use of lab testing to inform drug therapy, whether in companion diagnostics, pharmacogenomics or therapeutic drug monitoring. Indeed, although over 95 percent of

clinicians said in a survey that they know genetics affects drug response, only a small percentage said they have used genetics to aid drug therapy in practice. The number one challenge they cited is needing guidance to translate genetic results into clinical actions.

Physicians need better access to clinical decision support and access to genetic counselors who can help them choose the right test, interpret the results and explain them to the patient. Here we encounter a second major obstacle to PM: the restrictive view of payers about genetic counseling. Again, doctors say they don't know what tests to order or how to understand them; genetic counselors are degreed professionals trained to help with these issues; yet payers don't pay appropriately for genetic counseling services (if they pay at all) and, to my puzzlement, won't allow LabCorp genetic counselors to assist physicians because they say we have a "conflict" in that our genetic counselors would try to generate more orders for genetic testing.

I submit that part of the problem here is a lack of understanding about diagnostics. A diagnostic is not just a test that one decides whether to cover and pay for. A diagnostic is a complex system of reagents, instruments, software, algorithms, procedures, interpretations and support services, all of which must be included — and done correctly — to make the final product valid and clinically meaningful. Genetic counselors are part of the diagnostic service we offer; their code of ethics specifically forbids exploiting clients for personal or institutional advantage; and I can tell you from

personal experience that they would never encourage ordering tests that would not benefit their patient.

So physician awareness and underutilization of the skills of genetic counselors are obstacles. As I said, however, Ms. Kilmer was fortunate: she had the laboratory test. In doing so, she took advantage of next-generation sequencing (NGS), one of the major opportunities for PM. NGS is absolutely at the forefront of innovation; it has revealed the complexity and commonality of molecular alterations in various cancers, allowing the development of testing panels for frequent and actionable variants. NGS has also improved the accuracy and limits of detection for finding somatic mutations and can interrogate hundreds of genes for various alterations, including single nucleotide variants, small insertions or deletions, copy number variants and translocations. This innovation translates into enormous potential for non-invasive prenatal testing (NIPT) using the mother's blood to detect fetal chromosomal abnormalities, as well as potentially accelerating the detection of cancer and monitoring its progression through cell-free DNA circulating in the bloodstream rather than through invasive biopsies with variable accuracy.

Yet the opportunity of NGS runs into the third major obstacle to PM: payer coverage. A spokesperson for America's Health Insurance Plans (AHIP), a trade association for managed care plans, commented in the KHN story that recent scientific advances in genetic testing and genome mapping are

“remarkable and noteworthy,” but that AHIP needs a more definitive answer to how genetic testing truly ties to informing care and improving health outcomes. Interestingly, in March, Medicare announced it would cover NGS for certain advanced cancers when the test is an FDA approved or cleared companion diagnostic with an FDA approved or cleared indication for use in that patient’s cancer, or a Medicare Administrative Contractor determines that coverage is appropriate.

By contrast, consistent with the AHIP response, commercial payers have been mostly unreceptive to paying for genetic testing, particularly when performed by NGS. In our experience, payment for genetic testing in breast cancer patients is largely limited to BRCA 1 and 2 mutations. Adding genes beyond these traditional ones sharply reduces coverage. Ms. Kilmer’s mutation is in PALB2, a protein that binds to and colocalizes with the BRCA2 early onset protein, and may function in tumor suppression. It is not, however, part of the standard BRCA 1/2 test.

I did some research on the South Dakota State Employees’ Health Plan and discovered that there are six criteria for covering genetic testing. The fourth criterion is: “The testing method is scientifically proven to be valid in detecting the specified gene and the relationship between the gene and treatment have been validated through randomized control trials and presented in peer-reviewed scientific literature demonstrating health outcomes will be improved.” Given this, I venture to say that Ms. Kilmer’s test was not covered and that few genetic tests would be.

[Demonstrating that the relationship between the gene and treatment has been validated through randomized controlled trials is problematic in the first instance; randomized trials are designed to prove the safety and efficacy of drugs and devices, not the validity and utility of diagnostics. Given the small number of patients involved in most personalized medicine applications, a randomized trial – even if meaningful – would be enormously expensive to conduct and take years to conclude. Imagine the difficulty in then securing publication of the results in “peer-reviewed scientific literature demonstrating health outcomes will be improved.” In my view, the coverage criteria are heavily stacked against diagnostics – and therefore against patients as well.]¹

The focus in the coverage decision on how genetic testing improves health outcomes (demonstrated through the just-discussed requirement of randomized controlled trials published in peer-reviewed scientific literature) is really a way of asking the question: what is value? Of course, a genetic test alone is not going to improve health outcomes; the potential of personalized medicine is that the insights from the test and the actions taken as a result will do so. So the value question begins with a false premise that invariably leads to the misleading answer: “no, the test does not improve health outcomes.”

¹ *Bracketed remarks were not delivered verbatim. They are included here for clarity.*

But let's assume there could be a meaningful inquiry about the test result alone. If a companion diagnostic indicates that the patient will respond to a drug that is FDA-approved for the indication, does that improve health outcomes? If the test indicates that a patient will not respond to the drug – does that improve health outcomes? What would be covered? And how will a test that is intended to identify a small group of responders meet Ms. Kilmer's insurance company's requirement of validation through randomized control trials that will be nigh impossible to conduct, much less to secure peer-reviewed publications?

And there is more. What set of patients should we look at to determine value in the precision medicine calculation? We know how to measure quality-adjusted life years saved, but these assessments are typically made across a population, not at the individual level. How should such concepts apply to Ms. Kilmer or people like her when the idea of precision medicine is individualized treatment for a particular disease? Can we meaningfully characterize patient groups for which PM treatment will be cost-effective given the genetic heterogeneity of the U.S. population? How do we think about value when a drug that is indicated by genetic testing as one the patient will respond to can be thwarted by intra-tumor heterogeneity? This concern is particularly acute given the “hope or hype” debate about PM and policy questions about whether society can realize more value from addressing social determinants of health such as diet, smoking cessation and weight loss than from PM.

Parenthetically, innovative NIPT faces similar obstacles; payers limit coverage because they don't want to incur the cost of testing for the average-risk population. Yet we know that the incidence of microdeletions in the average-risk population (those women not considered high-risk) is significant, that they are detectable by NIPT, that NGS will continue to refine our understanding of those risks, and that NIPT is the safest and cheapest way to do this. The difference in viewpoints about the scope of coverage for NIPT is essentially a difference in perspective on how we define value of diagnostics and value of PM. Unless we come to some agreement among stakeholders about how to solve these admittedly difficult questions of assessing value, we will have a difficult time realizing the full potential of PM.

Ms. Kilmer's personal perseverance highlights another important opportunity for PM: the growing role of the consumer. The increasing use of non-disease-oriented, consumer-initiated testing will lead to better patient understanding of disease-oriented diagnostics and a reduction of the information asymmetry between patient and doctor. I support this trend, I applaud it and I think it is one of the most important things that is going to happen in PM in the next five to ten years. The prevalence of patient support and advocacy groups, opinions from "Dr. Google" and social media generally will democratize the understanding of disease treatment and progression.

Yet this opportunity also presents critical challenges to the credibility of PM. Having taken a few of these consumer-initiated tests myself, I can say unequivocally that the results are usually ... equivocal.

I recently took a test to determine my fitness level and the report I received stated in consecutive paragraphs: “People like you are more likely to have greater endurance for long-distance sports,” followed by “You’re more likely to have a harder time excelling at endurance sports. This is due to a genetic disadvantage in endurance and muscle efficiency caused by lower blood flow.” But wait ... two paragraphs later: “People like you may have greater blood flow to your muscles and therefore more strength, which is especially beneficial for exercises that require power over endurance.” What to do? Quit exercising? Quit taking over-the-counter tests?

This test is by no means alone in the market. One of my colleagues has tried essentially every in-home test available to consumers – some of which are clinically-oriented, some of which are not. Having reviewed the results, I can say without equivocation that analytical precision, reproducibility and concordance with gold standard reference lab testing is lacking in many consumer offerings. Scientific evidence for testing such as “food sensitivity,” “sleep and stress,” and “egg count” is scant, if it exists at all. And yet, as we think about PM and clinical trials, the validity of the data is fundamental. And as we move further away from the gold standard with wearables and in-home testing, I don’t in any way want to suggest that these are not important and valuable trends, but we need to be aware that they have brought into question the credibility of our field. Yet the consumer, the provider and the healthcare

system all assume that lab data, however obtained, is both clinically valid and accurately measured. The lessons from a blood testing unicorn of recent memory do not seem to have been fully absorbed.

I will say: precision, reliability and reproducibility of data are absolutely critical if we are to improve the delivery of care (whether through PM, clinical trials, value-based care or simply the routine encounter in the physician office), and in my judgment, the assumption that the results from any test ordered online are accurate is not a well-founded assumption. The FDA has said: “A bad test is every bit as bad as a bad drug.” Truer words were never spoken.

Finally, let’s talk about the manufacturer’s reaction to the publication of the story. This too is fairly typical of PM: the plight of a gravely ill patient is highlighted in the media and the “bad guy” caves in and pays. I’m not saying by any means that Ms. Kilmer should have been denied the drug — indeed, the article suggests that it is critical to her survival. I am saying that this type of decision-making process undercuts our ability to realize the full potential of PM. And it is particularly acute in oncology, where the media regularly publishes stories about decisions by insurers or drug companies to refuse to pay for therapy. In many cases there is no clinical evidence supporting that therapy and in some diagnostic testing has even determined that the patient will not respond, but the narrative typically includes emotional vignettes and a quote from the treating physician that the patient “has run out of options and needs a chance.”

This is not the promise of PM. The promise of PM begins with administering the right drug to the right patient, but it does not end there. That is a short-term win but not the long-term vision. To illustrate my point, let's move away from PM applications for oncology because the critically ill patient with no other treatment option clouds the picture there.

Think about a disease that causes much misery and decreased productivity, like migraines. Suppose there is a drug for migraines that is accompanied by a companion diagnostic. With consistent use of the companion diagnostic by providers and reimbursement by payers, we can: (1) get the effective drug to the patients who will respond to it and relieve their suffering, (2) identify the non-responders and use other treatments, and (3) use the non-responder patient set as the basis for research on and development of other therapies. Thus, PM creates a virtuous cycle: optimal patient care for responders, prompt exploration of alternatives for non-responders with cost savings from not using a drug that won't work, and robust discovery pipelines for new drugs. This model can be repeated for any disease state that is subject to exploration through genetic and biomarker discovery — although it will work best for those in which the stakeholders are not faced with a decision to “give the patient a drug or let them die.”

To summarize the PM equation: we have the challenges of physician understanding, accurate interpretation of test results, coverage and the determination of value, and confidence in the results. On

the other side of the equation, we have the opportunities of technology such as NGS, better utilization of genetic counselors, expanding knowledge bases and the ability to broaden the application to new disease states. Here then is my “short list” of things we need to do to make the potential of precision medicine a reality:

- Close the educational gaps for the key constituents and stakeholders:
 - Consumers
 - Providers
 - Payers
 - Other thought leaders
- Convene a cross-disciplinary group of interested parties to agree on the value equation:
 - How do we define the value of PM and how do we determine it in individual cases?
 - How do we balance the potential of short-term cost increases due to deploying expensive drugs versus long-term savings from avoiding ineffective therapies, providing better treatment and improving outcomes?
 - How do we assess the value of PM in the hierarchy of other healthcare initiatives?
- Through appropriate diagnostic-specific policy balancing innovation and access with patient protection, get serious about requiring:

- Scientific basis for tests
- Clinical relevance to the question we are trying to answer
- Reliability and reproducibility
- Expand the case for personalized medicine beyond oncology and create the virtuous cycle of effective treatment for responders, alternative treatment for non-responders and exploration of new treatments.

From my perspective, it is an exciting time for PM. We have made great progress, yet in my judgment we are still closer to the beginning of the journey than to the end. The opportunity ahead is enormous and I hope that we will find the will, the alignment of interests and the focus needed to complete the journey and keep the promise.