eye for pharma

PERSONALIZED MEDICINE IN ONCOLOGY

- Key insights from America's most respected oncology experts
- Get expert insight into how the reimbursement landscape will change for personalized medicine, with top challenges for payers revealed
- Discover the key challenges for personalized medicine regarding biomarkers, data and clinical utility

Featuring Exclusive Insights From:

- Dr. Ira Klein, Chief of Staff to the CMO, Aetna
- Dr. Bruce Feinberg, Chief Medical Officer, Oncology, Cardinal Health Specialty Solutions
- Dr. John Sprandio, MD, The Oncology Patient Centered Medical Home

With thanks to our expert thought-leaders, including:

- Dr. Ira Klein, Chief of Staff to the CMO, Aetna
- Dr. Bruce Feinberg, Chief Medical Officer, Oncology, Cardinal Health Specialty Solutions
- Dr. John Sprandio, MD, The Oncology Patient Centered Medical Home
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Personalized Medicine in Oncology

Introduction

Personalized medicine has become a buzzword in Oncology, but discerning the real meaning behind this hype, and the immediate practical implications for healthcare stakeholders, is difficult. Have we really arrived at a golden age for medicine? Will we actually see a radical improvement in the quality of care delivered to patients? Who pays for this revolution in innovation? These are some of the big picture issues dominating industry conversation on this topic, and indeed, each question deserves lengthy consideration in isolation. Focusing on the most important outcomes, this paper will seek to provide clear answers to these important questions.

We have enlisted the assistance of a number of Oncology experts and asked each what personalized medicine means to them, what they deem to have been the greatest commercial breakthrough in Oncology and how this practice area may evolve over the next five years. Beyond this, we interviewed each stakeholder on their perspective of the increasing challenge of working with and validating increasing flows of information from companion diagnostics and innovative products. We surveyed the opinions of key industry and diagnostic manufacturers (whom for approval reasons must remain anonymous), in addition to leaders from a leading Oncology publication, a pathways provider, Oncology patient-centered medical homes and a payer.

Personalized Medicine or Precision Medicine?

For the purposes of this paper, we shall define 'personalized medicine' as follows:

"Personalized Medicine" refers to the tailoring of medical treatment to the individual characteristics of each patient…to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment."

Report of the President's Council of Advisors on Science and Technology, September 2008

Dr. Sprandio believes that most clinicians, even non-oncologists, because of the uniqueness of every patient and the uniqueness of patient preferences and patient conditions, already deliver personalized medicine. So what do we mean by this term?

The phrase 'personalized medicine' has become more popular because the diagnostic testing allows a deeper exploration into the molecular basis of some diseases, both malignant and non-malignant. In oncology 'personalized medicine' has attracted attention due to the large number of new drugs and developments, driven by scientific breakthroughs over the last 40 years. Now all of that effort is coming to fruition in the form of drugs that are more targeted and potentially more effective and helpful to people. Sprandio suggests, that 'personalized medicine is the goal a lot of physicians wake up with every morning.' The ability to deliver personalized medicine is going to be strongly enhanced as the diagnostic studies are refined, more widely available and become increasingly matched with drug development.

Although this is the meaning that many in the industry have absorbed, there are those who disagree with this association and the term 'personalized medicine'.

Dr. Feinberg contests that a more appropriate term would be 'precision medicine.' His argument is that any form of management governed by precision should enhance healthcare outcomes through better design and greater accuracy. Whether this is through using a robot in surgery or through molecular diagnostic testing, the medicine should create enhanced outcomes.

Some may suggest that this implies a mere semantic distinction between personalized medicine and precision medicine. However, Dr. Klein offers further clarification. Personalized medicine reflects the extraction of genomic information that tells people about hereditary tendencies toward illnesses that could be prevented with lifestyle changes. In contrast, 'precision medicine' can be understood as the elaboration of the genetic makeup of tumors to allow people to attain better, more precise therapy.

If we accept the most basic definition of personalized medicine: 'the tailoring of medical treatment to the individual characteristics of each patient,' you could argue that most clinicians, even non-oncologists, because of the uniqueness of every patient and the uniqueness of patient preferences and patient conditions, already deliver personalized medicine. The reason that personalized medicine has taken such a hold as buzzword, seems more a product of it being an easy-to-sell, easy to commercialize term.

Will Personalized Medicine have a Positive or Negative Effect on Healthcare Stakeholders?

Our interviewees held consensus that ultimately, this question should be considered in light of one stakeholder, the patient. As we transition into personalized medicine, patients will experience clear improvements in the delivery of their care. Firstly, it will obviously give them access to therapeutics with greater efficacy and better outcomes, but there is also a key second point too. As we develop a deeper understanding of what works and what doesn't, we will also remove key fears around toxicity and eliminate situations where the patient is receiving care which could be having no impact or a potentially harmful impact. In terms of 'are there any stakeholders that stand to lose in this drive towards more personalized or more appropriate therapy in oncology?' There really aren't any stakeholders that stand to lose. Patients stand to gain, providers stand to gain because their decisions will be more effective and the pharmaceutical industry will stand to gain as they develop medications to match the molecular breakthroughs.

The key risk for pharma would be if they had a product which doesn't really set itself apart and deliver on increasing standards of innovation in an era of personalized medicine. Dr. Feinberg notes that if we consider the products already on the market, this becomes somewhat problematic. For many of these therapeutics the original basis for adoption was based on conducting large studies with very small potential benefit in progression free survival as a definitive outcome. If a more 'personalized based' use would define a population that would have much greater benefit, but be significantly smaller, then it would clearly have a negative impact on sales, but a positive impact on the patient population improving. A clear example is the KRAS inhibitors in the treatment of colon cancer prior to and following the use of KRAS testing.

However, Dr. Feinberg highlights a misconception about personalized medicine, which would suggest that stakeholders don't have reason to be fearful. The market is unlikely to transform overnight, the number of new molecular diagnostics which impact therapeutics being FDA approved remains around one per year. With this in mind, and in light of the current standards for clinical utility, the facts seem to point towards a very, very slow slope of change in this space. The rate of new drugs entering the market is vastly higher, and with the parallel depth and robustness of the pipeline this is unlikely to change. If you look at an example disease, multiple myeloma, which represents one per cent of adult malignancy, seven new drugs in phase three testing, two of which have already been approved in the past year. The rate of new drugs entering the market will be far greater than the rate of precision diagnostic tools restricting use of this new drug, therefore the likelihood of patients facing restricted access to these therapeutics by payers is very small.

Our industry stakeholder cautioned against complacency though, warning that change can be hard sometimes, especially if you have an organization that either isn't geared up for that or doesn't want to admit that change is underfoot. The only stakeholders, whomever they may be, that could stand to lose are those that don't recognize the strategic importance of finding a way to embrace this. If you were a pharmaceutical organization and you took a limited impact, broad population-based approach to your therapy, versus a high impact, smaller population-based approach; your pipeline may be at risk in the future. Eventually it could be likely, if not absolute, that a payer or HTA would determine it was not cost effective and/or not feasible for a tier 1 or tier 2 formulary and then the efforts associated with that would leave you in a space of diminishing returns where you could have taken control of the situation and made it more impactful for you from the start. Proactivity seems a preferable option to reactivity.

What was the biggest commercial breakthrough?

Perhaps because 'personalized' medicine has become a buzzword, we are fooled into the romantic notion of thinking that we are in the middle of some sort of technological revolution. If we cast our eyes back to the past however, the innovative process has been iterative, and possesses about 50 years of legacy. Some points of this history do stand out however, perhaps partly due to their importance at the time. Dr. Feinberg admits, "I struggle with this [pinpointing the biggest commercial breakthrough]. They are all advances. I think that the earlier ones are those that had the greatest meaning because they have redefined the way we think about oncology today."

One key definitional point in history is Gleevec. Arguably, the entirety of modern understanding of the impact of molecular diagnostics and genetics on cancer began with the identification of the Philadelphia chromosome. However, not all of our interviewees were in agreement. Dr. Sprandio noted the point of view of the oncologists; most believe they have been delivering personalized medicine ever since the availability of ER and PR status for breast cancer. Dr. Sprandio went as far as to define the greatest commercial breakthrough as "obviously the technology that is able to sequence in large numbers of genes and the potential availability of a great amount of detail with different individual patients' tumours." This technology has seen content acceleration even in the past three or four years, and this acceleration is not showing any sign of abating. Whether this going to be a commercial breakthrough in terms of commercial success remains to be seen, but you could define the possession of this ability at the same time as having a large number of drugs coming through that are more targeted to molecular abnormalities or protein abnormalities as a commercial breakthrough in and of itself.

What will Oncology Look Like in 5 Years?

"More targeted therapies with greater efficacy and less waste"

Dr. Ira Klein

A concise statement from Dr. Klein, that perhaps we can all agree with. But to what extent will we have more therapies and what will greater efficacy look like? Given that we have established an idea of the process of innovation as incremental, it would seem logical that we can't expect any huge surprises over the next five years or so. The pace is such that a future where 100 per cent of patients have their cancer care managed by a personalized approach seems a little further away than five years. If the pace of current innovation continues, the likelihood is that we will have continual evolution, with shorter and shorter timing between milestones over the next five years.

One viewpoint is that the greatest breakthroughs over the next five years won't come from innovative new products, but from making better use of existing science. Dr. Feinberg, suggests that, 'we think about the drugs that have the greatest use, that have non-inconsequential toxicity profiles and understand how we can use them better than we currently do.' The controversy surrounding Avastin is a clear example of this. Many practicing Oncologists were convinced that they were treating patients who were gaining benefit. This hints towards the possibility that there are other populations that could benefit from a better understanding of therapeutics available. Another example is Herceptin. If the industry had not been testing for HER2, then Herceptin may not have been approved for use across the entire population of breast cancer, which would have denied transformative treatment to many.

The delivery of care revolution

The positive innovation taking place within Oncology is not confined to what we are now able to treat with targeted therapies. Care delivery is also undergoing a revolution, which our demands attention. Dr. Sprandio sees the future impact of data on the delivery of care to individual patients as one of the few things which has the potential to re-shape Oncology care within the next 5 years. The influx of data will change the trial and error methods that oncologists are forced to use now in the absence of evidence-based data, and so it will change drug selection.

The Oncology patient-centered medical home model has shown positive indications that the possession of data generated from certain performance metrics in the execution of care greatly improves the Oncologist's ability to deliver consistent, of quality of care. Dr Klein agrees that data will be a big part of the future. 'The biggest breakthrough in Oncology in the next 5 years will be when we all actually learn to share the data.' This said, possessing the data and sharing the data that is going to be derived from molecular studies and new pharmaceutical trials is just one part of the picture. The real question that must be asked is how do you actually use that information and make sense of it.

Personalized Medicine and Reimbursement Policy in the USA

Payers in the US, particularly in light of the Affordable Care Act, need to determine what role they're going to be playing on an ongoing basis in the healthcare system. As providers, hospitals and clinicians take on more risk and play a bigger role in the management of the administration of the care, they will have to understand from a payer perspective what new or enhanced role they'll need to play to help the overall vision. With this in mind, there is potential for large shifts in policy. If we consider the provision of coverage policy edict, for instance, it does not seem to make sense to have a fragmented coverage policy approach in tandem with the increasing synergies around risk bearing entities on the provider side. If they're providing the care and seeing the day-to-day treatment, we can ask the question, is there a role for the payer to have these policies? We could plausibly imagine a situation where the payer, in possession of consolidated data, lends their bioinformatics expertise while working with others in partnership.

While we can posit these scenarios, Dr. Klein raises some doubts as to how exposed certain payers are to the sort of factors that could create a shift in policy. Dr. Klein notes that 'Policy shifts will be slow from any and every payer because the drug benefit is often outside of the medical benefit.' In explanation, the fact is that payers don't always control the pharmacy benefits for large health insured customers, and this immediately raises questions over the impact that payers can have over what they don't control. Specifically with regards to Aetna, Dr. Klein also added some insight. Two thirds of their business is self-insured, so for plans to manage individual small groups, maintain a quality insured population and deliver pharmacy benefit, they may make some shifts. Due to the complexity of internal systems, the cost of change is dissuasive and could run into tens of millions of dollars. The requirement for large IT investment coupled with the cautious mindset of many payers to unknown marketplace responses could remain a key barrier to change, at least for the time being.

Key reimbursement and payment issues from a payer perspective:

1. The key issue is how you reward community oncologists for holistic care.
2. How to figure out the right actuarial value of a cancer bundle
3. How to integrate all oncology drugs in a pharmacy benefit with an overall cancer strategy
   - Dr. Ira Klein, Aetna

The pressure to deliver patient outcomes

While large-scale shifts in policy may seem unlikely, at least for the time being, there is still something that we can say about the drivers behind payer reimbursement policy. Dr. Sprandio believes that the key consideration will always be the patient, highlighting that, 'in the US and in every industrialized country there is always going to be a drive to provide beneficial care to patients and that drive is going to exist whether it is government run, a single payer system or a chaotic system like there is in the US. Over time, payers will gravitate towards a policy of making sure that appropriate patients are teamed up with appropriate drugs. In general, payers are going to be supportive of the cost of new diagnostic procedures, to a point. The burden is on the clinician, the providers and the drug developers to make a business case for the benefit that is derived from new drugs.' In short, if the burgeoning pipeline can deliver its promise of better patient outcomes through a 'personalized approach,' then there is always going to be pressure to reimburse the drug

What are the Key Challenges for Personalized Medicine Regarding Biomarkers, data and Clinical Utility?

With so much information, the key challenge is to discern what data is valuable and how value is being defined. If a patient is being kept in check with the management of their disease there is a cost associated with that. The question asked will be whether the cost offset of the patient not going into crisis mode is beneficial and how that benefit is being measured. The clear difficulty here is establishing some standards by which clinical utility can be defined.

On the question of introducing legislation as a means of creating some standardization, our industry stakeholder had some thoughts to share. They were uncertain whether there was a need for regulation, but if a centralized approach to coverage determinations and decision making developed, this would be a natural extension into the clinical utility definition, and create a universal standard. It is however absolutely critical for pharma to get this right, as Dr. Klein adds, 'almost all payers will say that they're not going to pay for a test that has these weak association linkages. We really need to see that this truly works on a one to one relationship.'

While we wait for such standardization to materialize, is there anything that pharma can do to help the oncologist make sense of it all? Yes, but it would require the partnership and participation of multiple stakeholders. A key part of this jigsaw would be patient advocates, due to their unique positioning as a central point of communication for other stakeholders. For pharma, it is important that they work to understand where the strongest leverage points are, in order to generate meaningful conversation on how to deliver better outcomes.

The key concerns for Oncologists surrounding data from molecular studies and new pharma trials:

- How do you actually use the data to improve the execution of care?
- How do you make sure that every patient who is a candidate for an appropriate new drug based on a molecular abnormality is appropriately screened?
- How to make sure that patients are going to be guided through procuring the drug appropriately?
- How are patients going to be managed expectantly in terms of any side effects with these medications?

- Dr. John Sprandio, MD, Oncology patient-centered medical homes

Oncology patient-centered medical homes

Dr. Sprandio shared some thoughts on how the data influx impacts him specifically as a practicing oncologist leading an Oncology patient-centered medical home. The oncology patient-centered medical home model is a framework, in which processes of care and evaluation are standardized throughout the practice, this is important if appropriate patients are going to be screened. As a tool the goals of the Oncology patient-centered model is to enhance patient access, enhance coordination and communication for each individual patient's care and track outcomes in terms of symptom management, overall survival and disease-free survival for every individual patient. As additional quality metrics or characteristics are identified through new data, these become inserted into the model. The data is then tracked by their ability to monitor and report a lot of that data to the individual physician. When new data or therapeutics become available this then gets inserted automatically into the standardized processes of care in the oncology patient-centered medical home model. The Oncology patient-centered medical home is therefore impacted by new data on an evolutionary basis. As previous noted, a key challenge for Oncologists is the task of being able to cope with the increasing influx of new data to arrive at consistent, rational decisions for the delivery of care.

Biomarkers

What about situations where biomarkers are not so well defined as others, or simply don't exist yet? How does that affect the attempts to make sense of clinical utility?

Dr. Feinberg refers to the basic statistical understanding of specificity and sensitivity, noting, 'If we look at the KRAS pathway of signaling within the cell, KRAS downstream is further modified by DRAS and P10. The question however, is whether it is being modified in a way that is both clinically valid and clinically useful to the practitioner, the patient and the payer with responsibility for managing the dollars.' Dr. Feinberg states that the data currently suggests that it's not and this is what will be thought about and will undergo design as we look at biomarkers. The capability of the host or the number of potential biomarkers is almost unlimited and so it is clear that there will have to be a lot of thought into where the low hanging fruit is. This decision and the selection of value propositions are being driven largely by pharma, but this is where Dr. Feinberg believes we shall start to see some change. In the near future we will start to see more selection being driven by health economics and outcome research.

Correctly identifying low hanging fruit will be crucial because, as Dr. Klein makes explicit, payers will not relax requirements for blue-sky innovation. He writes, 'our standards for biologic markers and genomics aren't any different from our standards for any other tests for therapy. We don't lower the threshold just because it sounds cool.' In terms of biomarker acceptability and reimbursement, payers will still demand analytic and clinical validity and enforce this through claims or clinical policies.

Dr. Sprandio identified one of the biggest challenges for defining biomarkers going forward as limitations that currently exist in possessing an adequate tumor bank for testing. Dr. Sprandio observes that, 'one of the huge advances created in the study of oncotype and KRAS is the ability to retrospectively review pathology samples in tumor banks, allowing us to advance this cause of medicine at a much more rapid pace than by conducting prospector randomized trials.' When we start to look at new markets, an obvious obstacle emerges; do we have adequate tumor bank material to do the testing? Sufficient material would be needed so that testers are able to examine the blinded straight population and un-blind in order to determine if that profiling met the criteria for clinical utility.

The future for Oncology and Personalized Medicine

"The area of personalized medicine is going to be the golden age of medicine."

Dr. John Sprandio

While there can be no doubt that the science in pharma has progressed to a stage where 'personalized medicine' is a tangible reality, our discussion has shown that this may be a little further away than the hysteria surrounding the term would have us believe. The reality is that change remains incremental and it will still be some time before every cancer patient can walk into their oncology practice and receive truly personalized care.

With that said, Oncology is in the midst of an extremely exciting time. The changes underway are generating genuinely positive outcomes, in which more and more patients shall share as time progresses. In addition, the strides that are being made beyond the laboratories, with the revolution in care delivery, are what define this era as one with special promise. Dr. Sprandio's inspiring work through his Oncology patient-centered medical homes and Dr. Feinberg's Cardinal Health clinical pathways program are just two of many initiatives aiming to reduce the cost-burden of healthcare by improving efficiency, and thus outcomes. When one looks at the full picture it is hard not to agree with Dr. Sprandio.

While these developments are undoubtedly promising, we should recognize the vast amount of work to be done in the area of data and clinical utility. Pharma's task should be to put in place a framework to define the validity of data and clearly state the value proposition of new therapeutics. Although support tools such as clinical pathways and Oncology medical homes pilots can help shape this and optimize treatment prescription, stakeholders must work together to build a coherent language and a system that works. Only then will the systems be in place to achieve the overarching goal: giving the patient the best possible chance of receiving truly personalized care.