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Personalized Medicine: A Patient Primer On Best Practice

by William Looney

Personalized medicine is focused on meeting patients' needs, but it also has the potential to transform the delivery and financing of health care. In Vivo probes the path toward meeting both goals in an in-depth interview with Eleanor Perfetto, SVP for strategic initiatives at the National Health Council, the DC-based patient advocacy organization whose members include groups representing 133 million patients nationwide.

- Tracking the patient perspective on personalized medicine is critical to pharma's success in commercializing new products.
- Patient advocacy groups have knowledge, access and expertise to surmount drug development process hurdles.
- Such groups can provide essential third-party validation of clinical outcomes relevant to the real-world standard of care.
- As interest grows in evidence-based "value frameworks" to guide actions on drug access and reimbursement, the addition of a broadly distinctive patient point of view will counter reliance on narrow economic criteria as the driver in decision-making.

Every missive, every map and model, on the evolving landscape of personalized medicine puts the patient at the center. Yet it's surprising that many patient advocates don't feel their perspective is adequately captured as this new treatment paradigm matures from a conceptual vision in the medical literature to an institutional reality at the point of care. One word defines what patient groups want from a system that promises the right medicine, for the right person, at the right time. That word is clarity – about the patient role in the way science and regulation are applied to develop new medicines and how commerce intervenes to set their value and access in the marketplace.

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The stake for patients in the process around both is self-evident – but will more clarity bring more clout in delivering the health outcomes that patients want most?

Certainly, the science on precision targeting of medicines to address a patient's unique genetic expression of disease has advanced faster than the institutions responsible for regulating approval, access and the administration of care. The first reliable scientific measure of personalization arrived back in the 1960s, with the introduction of the Kirby-Bauer test on individual patient susceptibility to different antibiotic drugs. Testing with genetic biomarkers emerged later, in the 1990s. Of the 22 novel drugs and biologics approved by the FDA in 2016, two – *Clovis Oncology Inc.*'s *Rubraca* (rucaparib) and *Roche*'s *Tecentriq* (atezolizumab)for cancers of the ovaries and bladder, respectively – were introduced to patients jointly with specific diagnostic assays to drive individualized immunotherapy decisions at the clinical level.

. Several other approvals, including *Sarepta Therapeutics Inc.*'s *Exondys 51* (eteplirsen) for Duchenne MD and *Biogen Inc.*'s *Spinraza* (nusinersen) for spinal muscular atrophy, also rely on a genetic ID of patients most likely to benefit. The FDA approved two additional diagnostic imaging agents designed to establish a specific treatment pathway in patients with rare neuroendocrine disorders and recurrent prostate cancer.

Nevertheless, the FDA has only recently moved to establish a mechanism for patient input in evaluating potential curative advances from targeted therapies. A series of pilot consultations with patient groups covering some two dozen disease areas led, in 2016, to the creation of a formal FDA Patient Engagement Advisory Committee. For the first time, the "patient interest" emerged as a certified stakeholder in the FDA institutional process. The DC-based National Health Council (NHC), which represents disease advocacy groups with a collective membership of 133 million patients with chronic diseases, is spearheading a coordinated effort to draft a series of draft FDA guidances to structure engagement by patients throughout the drug R&D life cycle. The objective is to encourage more cooperation between patients, industry and the FDA in defining what is most useful and appropriate in advancing timely drug evaluations.

Patient Pain Points

Some aspects of the push toward engagement are likely to be challenging for the NHC and other patient groups seeking a more prominent position at the institutional level. One is the growing desire of payers for hard evidence in proving a medicine actually works. Does this negatively impact the authenticity and passion of the individual patient's subjective experience of disease? Many patient advocates cite the disease experience as the defining characteristic of what it means to be a patient. Will payers and regulators bend to allow use of real-world qualitative measures such as patient reported outcomes (PROs) in clinical trials? While there is movement in this direction at the FDA, payers and the professional medical community remain skeptical of PROs as a benchmark of efficacy and value. Failure to resolve the ambiguity will continue to disincentivize the drug industry from investing additional resources to generate evidence beyond

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the randomized clinical trial (RCT).

At the same time, are patient groups ready to support what payers desire most in assessing a drug's value: head-to-head trials against competitor products relying on the same patient population? For most of industry, it's a bridge still too far to cross. Likewise, patients, payers and the industry face a discussion around the patient interest in having a vector of individual financial burden included when value is assessed on the basis of economic factors like price and cost.

As volume yields to value as the key criterion for determining access for a new drug in the marketplace, detailed, prescriptive frameworks are being developed under the sponsorship of a wide variety of stakeholders, from academia to insurers, professional associations and even industry – PhRMA itself is quietly constructing pilot value frameworks on drugs for rheumatoid arthritis and multiple sclerosis. Again, groups such as NHC contest being left out of the decision matrix and are pushing their own ideas on how value determination can be refocused more toward outcomes that deliver to patients.

Parsing The Value Question

But it's a fine line that has to be drawn between patient engagement and even tacit endorsement of access decisions that might make patient advocates culpable in limiting drug choices for the very patients they represent. The risk is considerable as these frameworks start making tough choices about value, like justifying a high-tier, high-cost formulary listing or even barring access to a new medicine entirely. Peter Bach, MD, director of the *Memorial Sloan Kettering Cancer Center*'s Center for Health Policy Outcomes, cited this dilemma in a March 8 talk at the annual *Cancer Progress* summit in New York, noting that if organized patient groups want "skin in the access game" it shouldn't be done by putting individual patients in the position of having to live with the consequences – like forgoing a child's future college tuition to pay for a medicine that offers one shot at saving a life. "Acting in this manner would be unconscionable for any organization purporting to represent the patient interest," he said.

To shed more light on the issues around a patient-centric agenda on personalized medicine, *In Vivo* spoke recently with Eleanor Perfetto, PhD, senior vice president for strategic initiatives at NHC and professor of pharmaceutical health services at the *University of Maryland* School of Pharmacy. Her assessment of the prospects for a truly patient-centered system of care? It's still a work in progress – but it's progress nonetheless.

Q In Vivo: For the past decade, personalized medicine has been cited as key to a reformed, patient-centered system of health care delivery. As a leading representative of the organized patient community, do you believe that all stakeholders in the system are now on the same page regarding what

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personalized medicine is and how it must be applied to improve the practice of medicine?

A Eleanor Perfetto: We must differentiate between three themes, each of which can be confusing in relation to the others. These are patient-centered care, personalized medicine and precision medicine. Patients do have a clear view of the concept of patient-centered care – it's when patients are engaged in their care as full partners, with a clear voice in decisions, working toward the goal of an outcome that is meaningful to them. Decisions are not made *for* the patient, but *with* the patient, who sits in the driver's seat. Personalized and precision medicine are terms that are often seen as interchangeable. We see it this way: precision medicine relates directly to activation of the genetic component in the diagnostic and treatment setting. For example, a new treatment might be found effective in a group of patients with a certain genotype. Personalized medicine combines the best of all worlds, with providers considering the whole patient around what we call the "chronic care trifecta" – the individual patient's views about his or her illness, goals of treatment and personal circumstances – along with reliance on biomarkers and genetic indicators applied in the administration of drug therapy. In that context, personalized medicine is always patient-centered.
The most important aspect here is the outcome of treatment relates directly to what is important to the patient, including factors like quality of life, well-being and functional physical and mental capacities. Patients are partners in care, not study subjects. And personalized means personal. It means having a conversation with the provider that directs treatment toward answering the question: what does health mean to me, the patient? What are the results I want to obtain from treatment? The answer does not necessarily relate to the state of the science. A therapy might be tailored precisely to an individual's genetic profile but that does not make it the exemplar of personalized medicine. To call it patient-centered, there must be a connection to the patient experience and what the patient desires as the outcome of treatment.

For other stakeholders, there is a similar understanding of how personalized medicine is supposed to work in the practice of medicine. But in our fragmented

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delivery system, perception is not always in synch with reality. For example, physicians see themselves as prime advocates for the patient, yet are often reluctant to yield their professional autonomy in return for higher levels of patient engagement. Nevertheless, I believe a broad societal consensus on the importance of personalized approaches to treatment is at hand. Science is moving in that direction and so too is the growing emphasis on value in the financing of care. You can't prioritize value without making the patient – the ultimate consumer of care – central to the process.

Q **To put it more bluntly, does everyone in our complex system of health care understand what you are talking about?**

A On a basic level, yes. But the messaging around patient-centered, personalized care could be more explicit. The conversation must be broken down into three easily explained concepts: patient centricity in administration of care; patient-focused drug development; and patient engagement in decision-making, at all levels. Once stakeholders commit to a common understanding of what these concepts mean in practice, the institutional agenda around personalized medicine can progress more quickly.

"Until recently, the industry did little to incorporate the patient view during drug development, especially at the early stages when crucial decisions are made in bringing compounds forward for human trials. Conversation on the benefit-risk calculation focused entirely on the science." – Eleanor Perfetto, PhD

Q **Is the biopharmaceutical industry actually talking to patients while new compounds are still being tested in the lab and in the design of clinical trials?**

A Until recently, the industry did little to incorporate the patient view during drug

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development, especially at the early stages when crucial decisions are made in bringing compounds forward for human trials. Conversation on the benefit-risk calculation focused entirely on the science. Today, the situation has reversed. Patients are being solicited to provide insights on what aspects of treatment for a condition need to be emphasized. "What is the impact of your disease on quality of life? What are the preferred outcomes you would like from treatment? Or, here are the side effects I would like to avoid." The input is guiding decisions on trial design that in turn shape the endpoints, indications and labels of an approved drug. This is a big step forward for patients, especially for those who currently have no treatment options. Genetic research is allowing physicians and patients to have that conversation I alluded to, with the result that the potential for a positive treatment outcome is statistically much higher. It's taken well over a decade to get to this point, but the important thing is we are looking forward, not backward.

The NHC is particularly excited about the changes at the FDA, where patient-centered drug development has an unstoppable momentum. The 2012 Prescription Drug User Fee Act [PDUFA V] for the first time required the FDA to solicit patient input in the drug development and approval process. The attitude at the time was that the provision to convene a series of "voice of the patient" meetings was a check-the-box exercise; nothing would change. Gradually, however, opinions began to shift and today we can say these encounters have proved their merit to FDA staff.

Q **What's on the agenda for the PDUFA VI legislation due for enactment by the new Congress later this year? Is there still a missing regulatory component in the patient engagement process?**

A The current PDUFA VI commitment letter, which at this point is only that and not yet legislated, mandates the FDA to produce patient engagement guidance on an annual basis. Institutionalizing the process is long overdue. Companies need more guidance on issues like how to engage with patients while avoiding conversations that might appear to be inappropriate communication before a drug obtains marketing approval. We have produced an *NHC white paper* on what we see as the key barriers to patient engagement in drug development and how to resolve them. A key hurdle is the absence of any guard rails around the communication between the patient

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community, drug developers and the FDA. But we are quickly overcoming that hurdle.

This raises another issue: methodology. It's important to identify the specific information that patients can and should provide to drug developers to ensure the FDA has what it needs to make a "patient-centric" approval decision. We need a framework that makes the process more consistent. Technology gives us new ways to achieve this without barring creative approaches to what stakeholders can bring to the table. A few weeks ago we released the first in a series of proposed language *"mini-guidance" documents* covering topics that we recommend be included in a comprehensive FDA guidance on the patient role in drug development. We are using this list to start a conversation for the FDA with our members and other stakeholders which we hope will inform the progress of the required PDUFA VI guidance documents.

Q **How does this work feed into the larger political debate initiated by the Trump administration on reducing the FDA regulatory burden on industry and helping to speed the approval of new drugs for patients with few other options? Are you concerned that patients will suffer if medicines are approved on safety grounds alone, with efficacy established through direct exposure to the marketplace?**

A Anything that, in the interest of speed, puts patients at risk – we are firmly against that. Most of this is a philosophical debate about whether the FDA is too prescriptive and risk averse in considering treatments that might help patients. There is no specific rule in play to suspend the FDA evaluation of efficacy with the current standard of evidence, so it is hard to respond.

Q **What about the larger context, in insisting the FDA incorporate real-world evidence (RWE) in its NDA review process?**

A The NHC is very positive about the discussions relative to the 21st Century Cures legislation enacted in December 2016. There had been some discussion that PDUFA VI would address this topic in a similar manner. Our position is RWE is a complement

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– not a replacement – to the randomized clinical trial study that remains the basis for FDA drug evaluations. If RWE can buttress the evidence FDA collects through traditional means, ease some of the burden in study design and administration, and help move innovation forward, all without impairing patient safety, then the patient community is going to be favorably disposed.

Q **All this new evidence tends to put more attention on patient quality-of-life issues. Is the regulatory and scientific community where it needs to be in relation to this critical metric?**

A The FDA is not tone deaf on the quality-of-life issue. It has an obligation to be strict on rigorous methodologies around clinical study endpoints – facts, not opinion, rule the day. The issue for them is not whether quality of life is *important*; instead, the issue is that quality of life is *hard to measure*. To the patient, it's balancing all data sources to inform and drive regulators toward the right decision. That's the job FDA is supposed to do. It cannot slack off on methodological rigor if it wants to retain the confidence of industry and the public. That said, we should never ignore information relevant to quality of life in actual clinical practice. It cannot be discounted as a guide to decisions just because it didn't emanate from the standard RCT.

"Companies have come around to the view that engaging patients is not just an expenditure that drives up development costs but a test run to guide the direction of everything from the trial protocol to the final market launch plan." – Eleanor Perfetto, PhD

Q **What is the current state of the patient community's relationship with biopharma companies? The state of play – the pluses and pain points?**

A I see an abundance of enthusiasm in companies about building a more patient-centered approach to drug development. Much thought is being expended on

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organizational changes to ensure the patient perspective informs the clinical development plan. Overall, however, I would say companies are still finding their way – change is always difficult. Business cultures are slow to adapt. For decades, the physician was the go-to target for drug developers. Scientists and researchers rely heavily on the literature of the laboratory and professional practice. That narrow orientation doesn't disappear overnight. But the necessary conversations are taking place and most patient organizations will tell you the dialogue with biopharma is improving at a very rapid pace.

The creation of patient advisory and focus groups in many companies has had a positive effect on what researchers thought they knew about the diseases they study. Instead of addressing it from a purely theoretical point of view, discussions with patients offer insightful details on how physical symptoms affect daily life, especially on functional capabilities that usually escape the scrutiny of clinicians. Slowly companies have come around to the view that engaging patients is not just an expenditure that drives up development costs but a test run to guide the direction of everything from the trial protocol to the final market launch plan.

Biopharma's heightened interest has increased the time and resource demands on patient organizations. Drug developers want patient input, whether it be joining a KOL advisory board or helping in trial subject recruitment. Our groups also collect significant amounts of data, which companies find desirable, such as in building customized patient registries to support their medicines. While the interest is welcome, there is a drawback in that it may deflect from the mission of these groups to serve their own patient population. Patient groups have to find a balance around that.

Q **What about the payer? How would you describe the state of the relationship between patient groups and those who pay the bills for medicines?**

A By and large, payers have been relatively slow to embrace the concept of patient centricity. There are popular misconceptions to be overcome: patients are emotional and self-involved; they are ignorant about balancing evidence with costs; they want every imaginable benefit or service associated with their condition. The reality is

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patients tend to be very grounded. If the case is made rationally, patients are eager to act rationally, especially when they are given information and a choice. No patient is interested in bankrupting the economy just to get treated. The problem is that payers do an inadequate job of answering the question that patients value most: what options do I have? Physicians follow the incentive of the payment system and tend to offer a standardized diagnosis and treatment plan without probing what the patient might desire in the long run. This approach does not allow for a conversation that ranges beyond a single solution.

A Not only is this at odds with the abundant evidence now available to inform health decision-making, it ignores the fact that today patients are assuming more of the cost of their care. Consumer out-of-pocket costs for medicines are rising due to increased deductibles and formulary co-pays in the major commercial plans. Payers have been slow to recognize that patients are also paying customers, with just as much interest in obtaining value for money as other stakeholders in the health care system.

It should also be noted that some payers are trying new programs that focus on patient-centric care. However, once again, the definition of patient centric isn't the one we'd like to see, with the patient treated as a partner rather than a recipient.

Drug Value: It's Personal, Patients Say

By William Looney

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In a series of meetings and workshops over the past 18 months, the National Health Council has developed a platform that consolidates the patient community's perspective on how to assess value in choosing among alternative therapies in biopharmaceuticals and other key health care interventions.

Read the full article here

Q **The "product value proposition" is the driving force behind the debate on managing the cost of biopharmaceuticals, with a growing array of institutional responses underway to help structure a consistent approach to determining the appropriate price for a branded medicine. The American Society of Clinical**

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Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), Memorial Sloan-Kettering Cancer Center and the Institute for Clinical and Economic Review (ICER) are leaders in this effort. What is NHC doing to shape this important process in a way that benefits patients?

A We are in dialogue with each of these groups. Progress has been made over the past year. The overall response has been positive in recognizing patients should be involved in the preparation of drug value assessments. But the debate is still in flux; we are nowhere near 100% in terms of agreement. At base, when the question is asked "yes, value, but value to whom?" we want the definitive answer to be, "value to the patient." Not everyone is fully on board with that.

To us, what matters is the breadth and quality of patient engagement with framework sponsors. We are, for example, not for just a survey of a population with the patient as a study subject. That is confining. Instead, patients want to be full negotiating partners and to have a seat at the table before decisions on value for products are made. The NHC has prepared a "Patient- Centered Value Model Rubric" that sets criteria for patient centricity and engagement in the design and execution of a value framework. (*See sidebar, "Drug Value: It's Personal, Patients Say.*") One of its key points, for example, is that assessment methodologies must be flexible to account for the heterogeneity of the patient population, in which disease affects each individual patient differently over time, throughout the course of treatment, and from initial diagnosis to recovery to long-term survival.

To capture this, the evidence base used for evaluation must allow for more diversity in sources of data. We need to move beyond just the RCT as the sole benchmark of performance because it fares poorly in measuring outcomes like quality of life, which provides significant insight when examined through the prism of the patient.

A third priority is transparency. Everyone should know the constituent elements of each framework, the assumptions that buttress the methodology, and how the model actually works in practice. To a patient, transparency is simple: where did the data come from and how did you apply it in making the decision as to the value of the product? And, most important, how can I apply it to my own situation, with my

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physician and caregivers?

Q **What success have you had in using the Rubric to shift these frameworks toward a more patient-oriented perspective? Where are you in the discussions initiated with ICER last September over its latest update to the ICER Value Assessment Framework?**

A We have a mixed reaction to the update. On the positive side, we are pleased to see a specific commitment from ICER to integrate patients in the evaluation process. The group is open to including more sources of evidence in the review protocols, including outcomes data that are important to patients. But we'd still like to see more detail on exactly how patient groups will be engaged, especially through actions that ensure the patient voice will be amplified at the earliest stages of a review, not at a later phase when patient input becomes essentially irrelevant. For example, we continue to believe every ICER assessment should publicly disclose comments submitted by stakeholders, including whether the information was used in the evaluation – or not – and why. Generally, however, the relationship with ICER is positive and progressing. I am confident we will find additional ways to work together going forward.

Q **What are the key remaining barriers to institutionalizing the patient role in value frameworks?**

A There is a disconnect between what we know is the increased contacts that patients have with these value framework organizations and what is codified in their rules and methodologies. Groups like NHC are helping to do the "matchmaking" between framework developers and the patient community, yet it is still hard to identify the level of engagement when reading the value assessment reports released to the public. The true patient contribution to the process is unknown or unclear in the documents payers and other key stakeholders read when considering what they should pay for a new medicine. Consistency among the frameworks in disclosing patient involvement would help a great deal. We'd like to see that change, and for there to be more transparency.

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Q **Is the focus on a generalized approach to value frameworks misplaced? Might it be better to tie this work to the mandates of the professional disease organizations responsible for operationalizing the science around a single condition or therapy area?**

A This is a complicated issue. It sounds logical to put decisions on value in the hands of those with real expertise in a defined therapeutic area. But in practice, introducing one framework for one condition imposes a daunting hurdle because one disease and one set of treatments is not a viable instrument to address the fact that most patients suffer from multiple co-morbidities. For an aging population with diabetes, hypertension or congestive heart failure, how do you create a conceptual framework to incorporate such a diversity of conditions and adjust the methodology to fit the circumstances of the individual patient? It's a bridge too far right now. I believe it will intensify as a problem if or when frameworks become an accepted standard practice in reimbursement and market access.

Q **Is the momentum behind personalized medicine unstoppable? Do you see any potential for backtracking from a patient-centric vision of health care?**

A This is no passing fad. President Obama's Precision Medicine Initiative [PMI] was the definitive signal that a personalized approach to medicine had finally achieved critical mass. Focus on the patient is becoming more mainstream every day. Regardless of what happens to the Affordable Care Act [ACA] under the new Trump administration, the defining questions of a reform agenda remain the same: how do we make our health care institutions more responsive to patient needs and views? How do we apply all the new science to target the right treatments for the individual patient? What medical practice policies and procedures will best drive outcomes in line with patient preferences?

It remains to us to debunk the persistent myth that personalized medicine is a cost driver, not a cost saver. We know that when patients are involved and have the best knowledge available about their own condition and options, they make the right choices. In many cases, the right choices are the least expensive.

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Q **Many observers of the biopharmaceutical industry note that the targeted therapies encouraged by personalized medicine can be very expensive. Will it become harder for patient organizations to make the case for personalized medicine if drugmakers continue to set high prices for medications designed for a progressively smaller cohort of patients?**

A Drug companies justify the prices they charge for a new medicine as the consequence of strict regulation and lengthy, high-stake investments in research. Truly egregious instances of pricing tend to come from smaller, renegade players rather than big pharma. Nevertheless, the industry has to do better in explaining why some drugs are priced at a stiff premium to the current standard of care. While some higher priced products have been shown to offer greater value to patients than standard of care, for others it is unclear. Greater transparency on pricing and insurance plan design is one way to address this.

I am concerned that attention to pricing could slow the progress we've achieved. If we lose our focus on patient-centered care, innovations that improve actual clinical outcomes will suffer. There will be fewer options for patients, particularly those with rare diseases. We should be creating a health care system that drives patients to higher value care and discouraging lower value care. Solving this requires a conversation more honest than what we as a society have conducted to date. And the critique must extend to other health interventions – a larger conversation than targeting a single new drug for scrutiny while other cost drivers in the overall system go untouched. It's easy to single out one factor. It's hard to solve the bigger problem. But the onus is on the industry to take more initiative.

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