

# A Review of Precision Medicine, Companion Diagnostics, and the Challenges Surrounding Targeted Therapy

In the era of a fully mapped genome, continued personalization of pharmaceutical and diagnostics development can only accelerate. Personalized/precision medicine's aim is tailored treatments – the right treatment, for the right patient, at the right time. However, the high cost of developing therapies for small populations, coupled with the costs of developing the companion diagnostic tests forces manufacturers to recoup development costs through increased prices across smaller volumes. Balancing affordability and access may jeopardize precision medicine's promising future. This article examines these issues while asking – can we ensure access to these therapies while also sustaining innovation?

By Michele Cleary



## INTRODUCTION

With the arrival of a fully mapped genome, precision medicines are entering the global market at an ever-increasing rate. These tailored therapies promise more efficient use of healthcare resources by targeting those patients most likely to respond to therapy. However, challenges abound due largely to their very high price.

Precision medicine treatments serve a very narrow population, making research and development investments enormous. For instance, recruiting enough numbers of trial participants within these narrow populations is often an arduous process. In addition, these products require companion diagnostic tests to target the responder population.

Clearly, these products can provide enormous benefits. However, the question of affordability is inescapable. Can regulatory and reimbursement structures sustain access and innovation? How personalized is too personalized?

This article examines some of the challenges surrounding precision medicines: the development of companion diagnostics, reimbursement structures, real-world data (RWD) needs, and future trends. The article closes by reviewing how ISPOR is supporting the widening acceptance of these products.

## PRECISION, PERSONALIZED, INDIVIDUALIZED

Precision medicine identifies biological information (genes, RNA/DNA, proteins) to stratify patients, targeting those patients most likely to respond to a specific treatment. In precision medicine, diagnosis and treatment are intrinsically linked. While this field has evolved under different names (targeted treatment, individualized care, stratified treatments), the current preferred term is “precision medicine.”

Precision medicine represents a significant departure from the trial-and-error processes endemic to empirical medicine. Under these traditional processes, prescribers select a product and dosage with limited biologic information, monitor treatment effects, and adjust treatment accordingly. For example, a provider may prescribe a broad-spectrum antibiotic until more precise culture data are received on the causal organism, and a more targeted antibiotic can be prescribed.

This approach is often characterized by high rates of ineffective therapies. One study found drug therapies were ineffective in 38% of patients on antidepressants, 40% on asthma drugs, 43% on diabetes drugs, 50% taking arthritis medication, 70% of patients with Alzheimer’s disease, and 75% taking cancer drugs.<sup>1</sup> Even if these therapies are lower cost relative to precision medicine therapies, ineffective treatments are tremendously costly—racking up additional costs for adverse events, ongoing testing, and disease progression due to forgone more effective treatment.

## BENEFITS OF PRECISION MEDICINE

With whole genomic data sequencing, new disease pathways are being discovered, new therapeutic targets revealed, adverse drug effects evaluated, and ideal treatment populations identified. Precision medicine treatment targets only responders,

meaning tolerability and treatment adherence increases. This, in turn, leads to improved health outcomes and, ultimately, more efficient use of limited health services. Shifting treatment emphasis from reactive to targeted, precision medicine can help control the cost of healthcare.

Precision medicine has revolutionized oncology care. Next-generation sequencing (NGS), sometimes associated with sequential single-gene testing, is used to identify multiple specific mutations in a tumor and inform the selection of targeted therapy. NGS identifies those patients most likely to respond to a given precision medicine treatment, thereby improving patient survival by avoiding fewer effective treatments.

While most precision medicine therapies have been within the field of oncology, precision medicine research is successfully expanding into other disease classes. Genomic-based research has made significant progress in tackling diseases of the cardiovascular system, central nervous system, and immune system, as well as tackling metabolic, respiratory, and viral diseases.

Various models suggest that these products will alter healthcare utilization patterns significantly. For instance, a Genomic Health study estimated a 34% reduction in chemotherapy use would occur if women with breast cancer received genetic tests of their tumors prior to treatment.<sup>2</sup> Annual healthcare cost savings have been estimated to total \$604B if patients with metastatic colorectal cancer received genetic tests for the KRAS gene and then were treated appropriately.<sup>3</sup>

## REGULATORY SUCCESS

These benefits may be realized soon as more precision medicine products gain regulatory approval. Last year, precision medicine products made up 40% of all new products approved by the FDA. The first new class of precision drugs—small interfering ribonucleic acid (siRNA) treatments—was also approved in 2018.

In addition, the FDA approved the first pharmacogenetic and cancer risk-related genetic tests for the consumer market. One, a limited BRCA variant test, measures breast and ovarian cancer risks. The second, a personal pharmacogenetic test, provides information about 33 genetic variants that may be associated with a patient’s ability to metabolize some medications.

## GROWING GLOBAL SUPPORT

Precision medicine has garnered significant legislative support globally, reducing roadblocks to patient-centered drug development. In the United States, the Precision Medicine Institute was launched in 2015 to support precision medicine research and patient engagement. The 21st Century Cures Act of 2016 gave the FDA the tools needed to accelerate precision medicine therapies by reducing regulatory requirements, recognizing new trial designs (adaptive, innovative platform), and facilitating the use of real-world evidence.

In the United Kingdom, precision medicine received endorsements at the highest political levels for more than a decade (eg, 2009’s House of Lords Genomic Medicine Report), leading to a national strategic vision presented by the Human

Genomics Strategy Group supporting the National Health Service's adoption of precision medicine. Australia has taken bold steps to integrate genomics into the Australian health system outlined in the National Health Genomics Policy Framework and the Canadian Institute of Health Research included precision medicine within its 2015-2019 strategic plans.

## THE CRITICAL IMPORTANCE OF COMPANION DIAGNOSTICS

Despite these achievements, the promise of personalized medicine—the right treatment, for the right patient, at the right time—will remain unfulfilled without strong support for companion diagnostic testing. Companion diagnostic tests detect specific genetic mutations and biomarkers in those patients who are most likely to respond to precision medicine treatment, thus reducing the number of patients treated.

Eric Faulkner, MPH, vice president and executive director of Real-World Medicine at Evidera and a recognized global thought leader in personalized medicine, noted that “it is the actual diagnostic-drug knowledge confirmation that makes it precision medicine.” Providers need to act on test results—prescribe the indicated treatment (or not, if the test does not indicate suitability)—in order to garner the benefit of the added information or clinical utility. However, genomic markers often have limited ability to predict treatment response. Says Faulkner, “We are addressing precision medicine like a rifle (accurate and precise). When diseases [often] have more of a shotgun issue going on—multiple biomarkers that may cause a preponderance of the actual disease effect.”

Some targeted therapies may ameliorate the disease but fall short of being curative. Many genetic disorders, even so-called monogenetic diseases, often have multiple variants that cause the disease. Even so-called monogenetic diseases often have multiple variances that cause the disease sequelae.

Faulkner continued, “In the early days of precision medicine, we were targeting individual markers— EGFR, ALK, HER2, etc. And that's still the preponderance of what's on the market. But where we are going, and we are getting closer and closer, is hitting a tipping point.”

He predicts larger-panel tests are entering the market—first in oncology and then expanding to other disease areas. “Where we are headed though is for a test to be administered at the time the patient is being worked up for diagnosis where we could test hundreds of different biomarkers. Those tests will redefine what good looks like in precision medicine once they gain full acceptability.

Next-generation testing (NGT)—larger-panel tests including dozens of common biomarkers are now more readily available, testing smaller samples for a wide array of markers in one panel. Faulkner sees NGT as the next frontier of precision medicine,

stating, “It's reconciling our ability to know more biomarker information and then how to pull it through to a patient's treatment approach.”

John Watkins, PharmD, who leads Premera's Biotechnology Initiative and serves on ISPOR's Personalized Medicine Core group, shared Premera's successful experiences with gene-expression panel testing in early stage breast cancer. He noted that tests identify women who do not need chemotherapy along with their surgery, as the cancer is predicted unlikely to return. “That gets us a much better picture than the older methods of evaluating risks potential. We now can identify a number of women who don't need chemotherapy.” He added, “We can also identify groups of women that previously would have been told they probably shouldn't get chemotherapy, but the tests results find genetic variants that predict higher risks. So that test enabled that considerable improvement in terms of fine-tuning our treatment of those patients.”

**The concern obviously, is that we are working with complex things that we understand only a small part of. That always carries risk. But that doesn't mean you don't go there; it just means that you just go with appropriate caution and be prepared for the results not to be quite what you expected.**

Maarten IJzerman, PhD, chair of Cancer Health Services Research at the University of Melbourne, shared his experiences with NGS panels in distinguishing cancer subtypes

and identifying appropriate treatments for a patient. “Finding new molecular operations that can influence treatment decision, I consider to be the value of that whole gene sequence,” he shared.

But will payers cover such testing approaches? Watkins warned, “Payers tend to resist testing a whole bunch of stuff that is not as easily actionable.” IJzerman echoed this concern, stating that “It's very rigid if you only reimburse a specific test or just the single gene panel that can be very restrictive into what actually is going on in clinical practice.”

## BUT CAN HEALTH SYSTEMS AFFORD THESE THERAPIES?

As stated earlier, precision medicine has the potential to make health systems more efficient by targeting treatments to only those who will benefit. Despite these potential efficiencies, reimbursement remains a challenge. While regulatory bodies are open to precision medicine (eg, 21st Century Cures Act), reimbursement bodies are less accepting. For example, Centers for Medicare & Medicaid Services (CMS) requires step therapy to get to newer targeted therapy in Part B drugs or decreased payments for many precision medicine diagnostic tests.

Lou Garrison and Adrian Towse shared their foundational thoughts on value assessment for precision medicine, stating, “A broader concept of value is needed in the context of personalized healthcare. ... The potential barrier posed by inflexible or cost-based reimbursement systems, especially for biomarker-based predictive tests. These personalized technologies have global public goods characteristics that require global value-based differential pricing to achieve dynamic efficiency in terms of the optimal rate of innovation and adoption.”<sup>4</sup> >

Value assessment frameworks (VAFs) are evolving to better quantify the value of precision medicine treatments. Faulkner recommends 9 core components that should be considered regarding value frameworks aimed at precision medicine:

1. Incorporating diagnostic performance
2. Aligning evidence and reimbursement for the test component
3. Clarifying acceptable study designs and evidentiary expectations for the test component
4. Clarifying evidence expectations for different diagnostic applications
5. Incorporating value of “ruling out” treatment options
6. Addressing next generation testing special considerations
7. Addressing adaptive trial designs
8. Addressing the potential to target multiple pathways
9. Integrating precision medicine with artificial intelligence (AI), machine learning, and decision support

The American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the Institute for Clinical Effectiveness and Research (ICER), and the National Institute of Clinical Excellence (NICE) all have developed VAFs to better serve the needs and interests of their stakeholders. These VAFs were shared during ISPOR's 2018 Summit.<sup>5</sup>

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**Real-world evidence is changing what good looks like in the precision medicine space**

Contrary to the reimbursement strategies for precision medicine treatment, reimbursement for diagnostics remains largely focused on costs rather than value. However, without sound reimbursement policies for precision medicine, access to these diagnostic tests could be threatened, increasing the likelihood of disease progression and side effects stemming from suboptimal treatments. Further discussion is needed regarding reimbursement approaches for these companion and complementary diagnostics.

**RWE MAY HELP ADDRESS THESE ISSUES**

The future of precision medicine—from product development to reimbursement strategies—is heavily reliant upon RWD. These data can reduce clinical and health economic uncertainty on an individual patient level and clearly show the promise of the diagnosis-targeted treatment tandem. Real-world registry data should inform trial design, including adaptive trials, where added information about benefit can help target the right populations as more data accrue.

Technology has unlocked large biological data sets—DNA/RNA sequencing, proteomics, metabolomics—combining with electronic medical record/electronic health record (EMR/EHR) data to enrich our understanding of disease states and biomarkers. Clinical trial simulations, biomarker discovery and validation, cost models—will all require large volumes of RWD linked to both clinical and laboratory information, particularly due to the smaller patient populations. Finally, evaluating the

impact of WGS requires both randomized clinical trial (RCT) data and RWD, as there is increasing evidence that health outcomes reported in clinical trials usually overestimate clinical outcomes achieved in the real world.

Faulkner reflected on the convergence of genomic data with real world evidence, noting a common criticism is insufficient information about the epidemiology of biomarkers—how it connects to what’s happening with the population. “Real-world evidence is changing what good looks like in the precision medicine space,” said Faulkner. “We are having a convergence of acceptance of real-world evidence, changing study designs, knowledge of biomarkers, the evolution of analytical data sources, including AI machine learning. A lot of this stuff is starting to converge.”

Ijzerman added, “The longer-term objective here is to track patients to reduce practice variation and maximize outcomes across care pathways. That requires a much more conclusive dataset of patient-reported data, but also remote, long-term tools that can incorporate in the registry data.” He said that the goal is to “... really see all the services that they receive throughout their cancer care. And that’s a longer-term goal. And that takes a bit of time to build those registries.”

**NEW GENOMIC DATA SOURCES**

Real-world data sets are helping populate clinical trials when clinical trial data are insufficient to inform outcomes for rare conditions. Genomic data can be strengthened by linking real-world, patient-level data to other data so that trends can be analyzed and incorporated into research and development, tracking outcomes over time to understand the real-world benefit of these treatments. Adjustments to regulatory indications and coverage decisions can be made in real time as more information accrues.

Some of the critical real-world data sources include genomic databases. In the United States, the All of Us Research Program collects genetic data, biological samples, and other health information from more than 192,000 people from all 50 states. The United Kingdom initiated the 100,000 Genomes Project to promote precision medicine research. Similar registries are being assembled in Australia and the Netherlands, some including tissue storage for future study.

**REAL-WORLD DATA AND CLINICAL UTILITY**

Watkins outlined a critical need for RWD in demonstrating clinical utility surrounding variants of unknown significance. “Usually, getting to clinical validity is relatively easy. Demonstrating clinical utility is very hard.”

Clinical utility refers to the systematic assessment of a test’s usefulness—the ability of a diagnostic test to prevent adverse health outcomes by informing better clinical decision making—balancing the benefits to risks. Data are needed to demonstrate both the benefits and risks accruing from positive and negative test results.

Per Watkins, “I am hoping that machine learning systems or artificial intelligence will enable us to identify correlations that

will be predictive of treatment outcomes.” However, he warned that we are a long way from being there at this point. “We need to be able to collect large databases in order to apply machine learning algorithms to be able to draw useful conclusions from that. And when you consider the number of different types of cancer, there are literally hundreds of variants that have been identified that they test for, some of which we don’t fully know the significance of.”

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### ISPOR CONTRIBUTIONS

ISPOR has been actively supporting the ongoing development and acceptance of precision medicine. ISPOR’s Precision/Personalized Medicine Special Interest Group has been highly active in evaluating research best practices, decision standards, and value assessment processes.

In its 2012 report, *Challenges in the Development and Reimbursement of Personalized Medicine—Payer and Manufacturer Perspectives and Implications for Health Economics and Outcomes Research: A Report of the ISPOR Personalized Medicine Special Interest Group*, the ISPOR Precision/Personalized Medicine Special Interest Group published its report evaluating key development and reimbursement considerations from the payer and manufacturer perspectives.<sup>6</sup>

In 2016, ISPOR hosted a forum, “Generating Evidence of the Added Value of ‘Precision’ Medicine,” presented by the ISPOR Precision Medicine: Assessing the Value Working Group of the Precision/Personalized Medicine Special Interest Group.<sup>7</sup> This forum introduced many core concepts surrounding precision medicine, its value in predictive analyses, best practices, practical challenges, and research priorities.

During ISPOR’s 2017 Annual International Meeting, the ISPOR Precision Medicine: Assessing the Value Working Group of the Precision/Personalized Medicine Special Interest Group hosted a workshop, “Are Payers Equipped to Assess the Unique Value of Precision and Personalized Medicine (PPM)? Analyzing Current Value Frameworks and Their Application Within the PPM Context.”<sup>8</sup> In addition to introducing the members and goals of the working group, the workshop provided an overview of the field of various value assessment frameworks currently considered.

In 2018, ISPOR hosted 2 events concerning precision medicine—the 2018 Summit on VAFs mentioned earlier and a session during the ISPOR Europe 2018 conference. During this latter session, the ISPOR Precision/Personalized Medicine Special Interest Group hosted a session, “Diagnostics Evidentiary Dinosaur Evolution: Conventional Health Economics and Market Access Approaches Vs. Advanced Analytics as the New Norm?”<sup>9</sup> which reviewed companion diagnostics and future challenges that these products may face regarding evidence expectations.

ISPOR retains a virtual collection of related *Value in Health* articles on its website.<sup>9</sup> This ISPOR Precision/Personalized Medicine Special Interest Group, together with the whole ISPOR organization, will continue to share their thoughts, concerns, findings, and challenges as this field evolves.

### CONCLUSION

Precision medicine is now transitioning to wider acceptance. As this field matures, considerable challenges surrounding clinical research, regulatory approval processes, and reimbursement must be addressed carefully to ensure patient access and sustainable innovation.

Progress may be slow. But as Watkins summarized the current state of the field, “The concern obviously, is that we are working with complex things that we understand only a small part of. That always carries risk. But that doesn’t mean you don’t go there; it just means that you just go with appropriate caution and be prepared for the results not to be quite what you expected.”

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Michele Cleary is an HEOR researcher and scientific writer with more than 15 years of experience in the healthcare field.