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POLICY PERSPECTIVES

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

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ABSTRACT

Background: Personalized medicine technologies can improve individual health by delivering the right dose of the right drug to the right patient at the right time but create challenges in deciding which technologies offer sufficient value to justify widespread diffusion. Personalized medicine technologies, however, do not neatly fit into existing health technology assessment and reimbursement processes. **Objectives:** In this article, the Personalized Medicine Special Interest Group of the International Society for Pharmacoeconomics and Outcomes Research evaluated key development and reimbursement considerations from the payer and manufacturer perspectives. **Methods:** Five key areas in which health economics and outcomes research best practices could be developed to improve value assessment, reimbursement, and patient access decisions for personalized medicine have been identified. **Results:** These areas are as follows: 1 research prioritization and early value assessment, 2 best practices for clinical evidence development, 3 best practices for health economic assessment, 4 addressing health technology assessment challenges, and 5 new incentive and reimbursement approaches for personalized medicine. **Conclusions:** Key gaps in health economics and outcomes research best practices, decision standards, and value assessment processes are also discussed, along with next steps for evolving health economics and outcomes research practices in personalized medicine.

Keywords: diagnostics, health economics and outcomes research, health technology assessment, personalized medicine, reimbursement.

Introduction

Similar to the positioning of Odysseus' ship between Scylla and Charybdis,[1] personalized medicine technologies are currently caught between expectations of improving health outcomes and uncertainty about navigating the rapidly changing regulatory and reimbursement environment. In an increasingly cost-conscious environment, in which health decision-makers are charged with making difficult decisions on the balance of costs and benefits, personalized medicine technologies hold the potential to improve health outcomes, provided that value for money can be demonstrated and data uncertainties addressed.

Personalized medicine has been defined in many ways [1–3]. For purposes of this article, the Personalized Medicine Special Interest Group (PM SIG) of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has defined personalized medicine as the use of genetic or other biomarker information to improve the safety, effectiveness, and health outcomes of patients via more efficiently targeted risk stratification, prevention, and tailored medication and treatment-management approaches. Although this article

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[1] Scylla and Charybdis are two monsters from Greek mythology viewed as virtually impossible for ships to pass between, as getting too close to either risked destruction of the crew and the ship.

touches on issues relevant to other diagnostic applications, our emphasis is primarily on pharmacogenomic or pharmacogenetic (hereafter labeled PGx) applications, in which use of a companion diagnostic informs selection or use of specific medicinal products.

Key challenges associated with PGx include translation of knowledge into clinical practice, lack of best practices for value assessment, and integration into evolving health care delivery models [4–6]. Potential benefits have also been characterized to include the following [1,7–10]:

- Increased certainty about diagnosis and mechanism of disease
- Improved estimation of patients' risks of later outcomes (e.g., prognosis), which could influence treatment management decisions
- Better prediction of response to therapy or drug metabolism rates or a reduced potential for adverse events
- Reduced wastage of health resources associated with treating nonresponders
- Improvement in the quality and cost-effectiveness of patient-tailored treatment versus empirical approaches to prescribing

Assessment of the added value of PGx approaches is complex and depends on many factors including the safety and performance of the diagnostic or treatment, biomarker prevalence, utility of the test for informing patient management, and the comparative effectiveness of the test-treatment strategy versus standard of care (SOC). As with any emerging technology scenario, clarifying areas of uncertainty and moving toward standard regulatory and reimbursement practices will facilitate the broader adoption of PGx into clinical practice [11].

Two of the stakeholder groups with significant influence on innovation and uptake of PGx technologies are the payer and the technology manufacturer (including both diagnostic and pharmaceutical developers). Payers include a wide variety of governmental and private organizations that manage reimbursement and access to patient care. They vary in size, scope, and the extent to which they manage or commission care. Some payers enforce strict coverage rules, while others allow clinicians a great deal of latitude to determine appropriate care for each patient. While regulators, physicians, and patients also influence the uptake of PGx, this article characterizes key issues associated with PGx from the payer and manufacturer perspectives, identifies key challenges facing them, and considers the role of health economics and outcomes research (HEOR) methods in addressing these challenges.

Methods

The ISPOR Board of Directors approved the formation of the PM SIG to develop a document on HEOR practices/considerations for diagnostics and personalized medicine in late 2009. Researchers experienced in this field and working in academia, research organizations, the pharmaceutical industry, or US or European governments were invited to join the Leadership Committee of the PM SIG. The PM SIG held several discussion sessions and conducted a review of the peer-reviewed literature in PubMed and The Cochrane Library and available gray literature to identify key issues related to HEOR and reimbursement of diagnostics and personalized medicine. The issues relevant to the article were presented for comment in 2010 at both the ISPOR 15th Annual International Meeting (held in Atlanta, GA) and the 13th Annual European Congress (held in Prague, Czech Republic). Drafts of the article were also sent for comment to the global PM SIG review committee, a leadership committee of 60 US commercial payers of the National Association of Managed Care Physicians, and the international Advanced Medical Technology Association.

Issues in Technology Assessment and Payer Decision Making

Choosing the best medicine and its correct dose for the individual patient remains a largely empirical process; clinicians prescribe treatment, observe the outcome, and adjust drugs and doses accordingly. It has long been understood that some patients respond better to certain therapies than do others, but it is difficult to know *a priori* which individuals will respond to a particular treatment. For payers, this uncertainty results in inefficiencies in selecting treatment, managing cost, and optimizing patient outcomes.

Payers in countries with formal health technology assessment (HTA) programs are increasingly likely to deny or severely restrict reimbursement of therapies when the clinical and/or economic value proposition for the broader patient populations is unfavorable, unclear, or unexceptional [12–16], as they seek to limit coverage of such therapies to subpopulations most likely to benefit. The potential of PGx to effectively target responders, improve outcomes, and reduce costs appeals to payers [4,17–19].

In principle, payers benefit from the availability of companion diagnostics that accurately identify responders, reduce the number needed to treat, and thereby improve the efficient use of scarce resources. Payers may also support tests focusing on safety—such as the test for the JC virus to identify immunosuppressed patients at risk for potentially fatal progressive multifocal leukoencephalopathy—if, by increasing the number needed to harm, testing is cost-effective for risk identification [20]. Payers may also consider the societal consequences of test-and-treat strategies and system integration challenges. Although payers recognize the potential advantages of PGx, they are also cautious regarding the potential downsides of this approach.

Emerging PGx technologies often involve gene-based and other molecular tests. Currently, single-marker diagnostics often have an acquisition cost of less than US $400 per patient. From the payer perspective, it is often considered a reasonable investment to determine whether a medicine with annual costs of $20,000 to $100,000 is likely to benefit a particular individual. The rapid integration of *KRAS, epidermal growth factor receptor (EGFR), and BRAF mutation* testing into clinical guidelines for cancer patients receiving cetuximab, erlotinib, and vemurafenib, respectively, provides key examples of rapid PGx uptake by payers across major health care markets. Pharmaceuticals that have launched with the necessary tools to locate responders have generally gained payer acceptance, for example, trastuzumab and imatinib [21–24]. The initial market failure and later reemergence of gefitinib with a companion diagnostic (*EGFR*) also illustrates payer willingness to accept scenarios for which the responder population is clearly identified [25–27]. Examples of marketed PGx tests and their intended use are highlighted in Table 1.

However, PGx scenarios are not always a guarantee of payer acceptance [28–30]. In a recent review of cost-effectiveness studies on PGx tests, Paci and Ibaretta [31] reported that 27% of studied tests had unfavorable or equivocal cost-effectiveness compared with SOC (although almost three-quarter of these were deemed cost-effective compared with SOC). Some diagnostics developed separately from the companion medicine (e.g., testing to inform warfarin dosing and CYP2C19 testing to identify clopidogrel [Plavix] responders) have not achieved broad payer acceptance because evidence of the links between testing, treatment, and health outcomes is not well established [32,33]. Payers must also consider unmet need and ethical issues in evaluating PGx, where a subpopulation-targeted treatment is identified but no effective alternatives exist.

Cost-effectiveness estimates for recent pharmaceutical-diagnostic combinations have been highly variable among major HTA markets, suggesting that methods for incorporating test information into economic evaluations are inconsistent. One example is *EGFR* testing before gefitinib trial. The manufacturer submitted cost-effectiveness