## 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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A B S T R A C T

**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.

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## 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

| Table 1 – Payer and health technology assessor questions to determine the value of test-treatment combinations. |
|---|
| Payer and HTA agency considerations |
| ▪ What is the accuracy of the test? To what extent are responders overidentified (false positives) or missed (false negatives) by the test? |
| ▪ Are the test results actionable? Does the result(s) lead to changes in clinical practice? Will physicians use the test to inform treatment selection or ignore results? What potential harms are associated with the test? |
| ▪ Is test interpretation clear? Are test results binary (i.e., yes/no) or is there an intermediate range of test results that may complicate physician acceptance of the test and enforcement of coverage policies that limit access to responders? |
| ▪ Are the test results actionable? Has a dosing algorithm (for instance) been developed, validated, and tested for effectiveness? |
| ▪ What is the clinical utility of the test (i.e., does use of the test improve health outcomes)? |
| ▪ Has an RCT been performed of a test-and-treat strategy versus standard of care? |
| ▪ How many tests must be paid for before one treatable patient or adverse event is identified? What is the number needed to test, the number needed to treat, and the number needed to harm? |
| ▪ How much more effective is the treatment in the responder population compared with standard-of-care alternatives? |
| ▪ What is the proper comparison strategy for a PGx test and/or medicine if others do not exist for that indication? |
| ▪ What is the budget impact of avoiding resource wastage by treating nonresponders with alternatives? |
| ▪ Based on the cost of the test and the associated treatment, what proportion of responders must be identified to make the PGx scenario clinically beneficial and cost-effective? |
| ▪ Should all patients receive the test before accessing alternative medicines in the same position (e.g., first-line vs. second-line) or formulary tier? How would this influence appropriate access? |
| ▪ How do we handle the multiple diagnostic tests that may emerge after launch of a diagnostics-driven medicine? What are the implications for their variable test performance on patient outcomes and cost-effectiveness? |
| HTA, health technology assessment; PGx, pharmacogenomic/pharmacogenetic; RCT, randomized controlled trial. |

estimates of £23,615 per quality-adjusted life-year (QALY) and the National Institute for Health and Clinical Excellence estimated cost per QALY at £35,700 while the Scottish Medicines consortium estimated £154,022 per QALY [25,34,35]. Clearly, best practices for modeling economic outcomes of PGx strategies are needed, including how to incorporate diagnostic characteristics (e.g., test performance and receiver operating characteristic curves) into sensitivity analyses and value assessments and address gaps or uncertainties in information related to the diagnostic test.

Our review identified many questions specific to PGx and/or diagnostics scenarios that payers and HTA agencies should consider (Table 2). Such questions have significant implications for HEOR and value assessment for PGx and underscore the need for adapted methodological approaches for diagnostics. Aside from emerging regulatory requirements [36], methodological approaches fall into two key dimensions: 1 framework for HTA and decision-making criteria and 2 level and nature of evidence that is required for HTA. At present, differing methodological approaches and experience with handling PGx may result in highly variable patient access decisions.

Payers also face broader challenges to decision making regarding PGx interventions. Key issues include uncertainties around

evidence assessment, gaps in the evidence supporting clinical utility and cost-effectiveness of diagnostics, when modeling is sufficient/possible versus when additional clinical evidence is essential to address uncertainties, applicability of risk-sharing agreements based on test results, variability in evidence supporting laboratory-developed versus regulatory-approved tests, insufficient communication between authorities evaluating tests and treatments, difficulty tracking diagnostic utilization, and lack of infrastructure or mechanisms to support or fund diagnostic testing [1,8,37–39]. In the case of clinical utility, for example, inconsistent definitions and availability of evidence and uncertainties regarding assumptions can compromise decision making [40]. However, payer recognition that numerous PGx technologies are in the pipeline has prompted HTA agencies and payers in some markets (e.g., Australia, Canada, France, the United Kingdom, and the United States) to consider implementation of more explicit decision criteria/guidelines, policies, and infrastructure.

## Issues Associated with Development of Pharmacogenomic Diagnostics and Treatments

Retooling pharmaceutical business models around targeted therapies has affected many aspects of the pharmaceutical development process, from research and development to reimbursement and market access. More than 50% of biopharmaceutical manufacturers have integrated PGx into development programs to better support product differentiation and market access potential [41,42]. As a consequence, patient subpopulations identified by PGx may be too small to be profitable. To balance smaller population sizes and growing development costs, pharmaceutical manufacturers have increased pricing for targeted therapies over the past 15 years [43,44]. Rising treatment prices have in turn spurred heavier payer scrutiny [45,46].

Many new PGx diagnostics are also more costly than historical and routine tests, often ranging from the low hundreds to the thousands for a few emerging multimarker tests (e.g., Oncotype DX, AlloMap, ChemoFX, and MammaPrint). At present, only a small number of PGx tests have become established in clinical guidelines (e.g., tests for *HER2* and *KRAS*), although many others are routinely used in practice (see Table 2). As the availability and cost of diagnostics have increased, payer emphasis on diagnostics has grown in tandem, pushing test manufacturers toward value demonstration approaches similar to those used for pharmaceuticals [9,47].

Differing business incentive structures between diagnostic and treatment manufacturers also currently complicate development and collaboration. Key challenges include markedly different reimbursement and market incentive structures, resources to support evidence development, and intellectual property protections [37,40,48]. The potential profitability of PGx may be influenced by factors such as budget constraints, rigor of HTA processes, reimbursement coding, population demographics, and growth and demand for new health services. In addition, many pharmaceutical manufacturers are still in the early stages of assessing the commercial implications of codevelopment and evolving infrastructure to support PGx.

At present, many uncertainties around PGx approaches remain from both the test and treatment manufacturers' perspective (Table 3). These uncertainties require manufacturers to consider the HEOR and commercial implications of biomarkers at every stage of the pharmaceutical life cycle. Both methodological and practical business challenges highlighted in Table 3 limit the degree to which diagnostics manufacturers can pursue evidence development initiatives similar to therapeutics. Uncertainties regarding clinical and economic evidence requirements, limited intellectual property protection, and lack of value-based payment remain the key hurdles to diagnostic commercialization. In addition, it can also be substantially more difficult to demonstrate the clinical utility of stand-alone tests, given current market incentives and lack of clarity on decision requirements. While codevelopment scenarios enable the diagnostic

| Diagnostic | Company | Intended use |
|---|---|---|
| **Table 2 – Examples of commercially available PGx tests and their intended use.** | | |
| Diagnostics for selecting patients for a therapy or informing therapy use/modification | | |
| AlloMap | XDx | To identify heart transplant recipients with stable allograft function to inform patient treatment decisions |
| AmpliChip CYP 450 | Roche/Affymetrix | To identify CYP variations to individualizing treatment dose for certain drugs |
| c-Kit pharmDx | Dako/Novartis | To identify patients with gastrointestinal stromal tumors eligible for treatment with Gleevec/Glivece |
| cobas 4800 BRAF V600 Mutation Test | Roche | To detect EGFR in colorectal cancer for Erbitux or Vectibix Rx candidates |
| EGFR | Dako, Zymed, Invitrogen, DxS/ Qiagen/Merck-Serono | To detect EGFR in colorectal cancer for Erbitux or Vectibix Rx candidates |
| HER2 neu | Dako, Abbott, Ikonisys, Kreatech Dx, Oncor, Invitrogen/Roche | To detect HER2 in breast cancer for Herceptin Rx candidates |
| KRAS | DxS, Qiagen, Transgenomic/ Merck-Serono | To detect KRAS in colorectal cancer for Erbitux or Vectibix Rx candidates |
| PGxPredict: CLOZAPINE | PGxHealth (clinical data)/Novartis | To ascertain the risk of clozapine-induced agranulocytosis (treatment of schizophrenia) |
| PGxPredict: Rituximab | PGxHealth (clinical data)/Novartis | To select patients with non-Hodgkin's lymphoma for rituximab (Rituxan/MabThera) Rx |
| Therascreen EGFR RGQ PCR Kit | Qiagen/Astra-Zeneca Qiagen/Boehringer Ingelheim | To detect EGFR mutations to select patients with non–small-cell lung cancer (NSCLC) for the tyrosine kinase inhibitor gefitinib (Iressa) or afatinib (TomTovok) |
| Trofile | Monogram/Pfizer | To test for HIV-1 coreceptor tropism; companion test to maraviroc (Selzentry, or Celsentri outside the United States) |
| Vysis ALK Break Apart FISH Probe Kit | Abbott/Pfizer | To identify the expression of an abnormal anaplastic lymphoma kinase gene for selecting patients with locally advanced or metastatic NSCLC for treatment with crizotinib (Xalkori) |
| Diagnostics to determine risk or prognosis | | |
| BRAC Analysis | Myriad | To detect carriers of BRCA gene mutations, at risk of breast and ovarian cancer |
| ChemoFx | Precision Therapeutics | To determine chemotherapy resistance |
| Familion | PGxHealth (clinical data) | To diagnose of 9 different familial cardiac syndromes |
| Femtelle | American Diagnostica (Sekisui group) | For prognosis of patients with breast cancer, to select patients most likely to benefit from chemotherapy |
| MammaPrint | Agendia (NL) | To assess a breast cancer patient's risk for metastasis |
| Mammastrat | Applied Genomics, Clarient | To classify individual patients as having the risk of breast cancer recurrence |
| Oncotype Dx Breast Cancer | Genomic Health | To predict the likelihood of breast cancer recurrence |
| Oncotype Dx Colon Cancer | Genomic Health | To predict the likelihood of colon cancer recurrence |
| Phenosense GT | Monogram | To check resistance to drugs for HIV |
| PreGen-Plus | Exact Sciences | To screen for colorectal cancer |
| Prostate Px | Aureon Biosciences | To calculate prostate cancer patient's probability of disease progression |

Dx, diagnosis; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; KRAS (or v-Ki-ras2), kirsten rat sarcoma viral oncogene homolog; PCR, polymerase chain reaction; Rx, treatment.

to establish a closer correlation between test use and health outcomes, questions remain regarding appropriate economic assessment methods. Some regulatory authorities, such as the Food and Drug Administration, have worked toward clarifying expectations around codevelopment scenarios [36]. Until these factors are addressed, they remain pivotal limitations to companion diagnostic innovation.

In addition to diagnostic considerations, pharmaceutical manufacturers must consider a host of new issues specific to codevelopment (see Table 3). From the manufacturer's perspective, decisions to pursue PGx development versus conventional "treat-all" approaches are complex and depend on many factors including patient population size, pharmaceutical cost (and patent status) and volume trade-offs, degree of payer management of the target indication, and potential for value differentiation [49]. Key uncertainties related to HEOR and market access include integration of

PGx into early "go/no go" decision models, best practices for integrating testing into clinical trials and economic models, implications of testing on reimbursement and uptake, PGx value communication, and uncertainty regarding test funding and the need for risk-sharing arrangements. Despite the availability of applicable clinical and economic methodologies for the assessment of medicines, significant room exists for the refinement of HEOR approaches tailored to address PGx issues.

## How HEOR Can Help Improve Decision Making Regarding Pharmacogenomics

Our SIG identified five key opportunities for the use of HEOR approaches to improve decisions regarding the advancement of PGx. This article focuses on key areas and topics where best practices

**Table 3 – Typical diagnostic and pharmaceutical manufacturer questions to determine the viability of pursuing PGx approaches.**

| Diagnostic developer considerations | Medicine manufacturer considerations |
| --- | --- |
| **Development considerations** | |
| ■ At what time in the pharmaceutical life cycle should test development begin? | ■ Is a biomarker required for success of the new pharmaceutical in development? Are single-marker or multimarker tests more likely to be supported by payers? |
| ■ What relationships with pharmaceutical manufacturers are feasible? | ■ Is the correlation between the biomarker and the treatment outcome clear or well understood? |
| ■ What intellectual property protection is available? | ■ What level of test performance (i.e., sensitivity, specificity, and predictive value) is required for a test-treatment combination to be viable? |
| ■ Will evidence development efforts pave the way for "fast follower" tests with lower hurdles to market? | |
| ■ Would a rule-in or rule-out test be most | |
| ■ important for payer and physician acceptance? | |
| **Evidence and HTA considerations** | |
| ■ What minimum test performance will be required to support the test? | ■ What is the optimal percentage of treatment responders required for physician and payer acceptance? |
| ■ What percentage of false positives and false negatives will jeopardize payer and physician acceptance of the test? | ■ How will HTA agencies and payers define clinical utility for the test application? |
| ■ What evidence is minimally necessary to demonstrate clinical utility? | ■ What clinical and economic evidence is required to support the biomarker test under a codevelopment scenario, and what type of study design is best suited to provide such evidence? |
| ■ What is the minimum evidence necessary to support reimbursement given the | |
| ■ limited potential for value-based pricing? | ■ What comparators are most applicable to support reimbursement of the test-treatment combination? |
| ■ How will HTA agencies and payers define clinical utility for the test application? | ■ How do differing HTA and reimbursement processes impact the likelihood of test and treatment acceptance? |
| ■ What economic data, aside from the cost of the test and budget impact, are essential for test acceptance? | ■ At what point does the cost of the test make demonstration of cost-effectiveness unlikely? |
| ■ What approaches to modeling clinical utility and cost-effectiveness will be acceptable to HTA agencies and payers (if any)? | |
| **Commercial considerations** | |
| ■ Are there barriers to physician adoption of the test (e.g., lack of familiarity, invasive testing method)? | ■ What are the implications of including the biomarker in the pharmaceutical label? |
| | ■ Will a biomarker strategy help or hinder |
| ■ Would the test solve a substantive decision problem or change patient management? | ■ commercialization? If so, how? |
| ■ What is the commercial potential of the test if the medicine fails? | ■ Under what circumstances will payers accept higher pricing given smaller market sizes associated with PGx approaches? |
| ■ How can we increase the likelihood that decision makers will support the use of our specific test versus alternative tests? | ■ Who should pay for testing—the payer or the manufacturer? |
| ■ What potential is there for value-based pricing of the test (if any)? | ■ Is there a role for risk-sharing agreements to tackle uncertainties around a personalized medicine? |

HTA, health technology assessment; PGx, pharmacogenomic/pharmacogenetic.

could be further developed or defined. These opportunities span the current continuum from early to later-stage decisions with emphasis on addressing key gaps associated with development, evaluation, and reimbursement of PGx technologies.

### Informing research prioritization and early value assessment

Two related approaches used in HEOR can inform the assessment of the potential value of PGx at an early stage and prioritization of further research: 1 early-stage decision modeling of potential cost-effectiveness and 2 formal value-of-information (VOI) analyses [50,51]. The foundation of many cost-effectiveness (and cost analyses, which we subsequently label as cost-effectiveness analyses because they have the same theoretical framework) is the construction of a decision-analytic model to estimate the projected or actual cost-effectiveness (or cost utility) of a new personalized medicine. These models can vary in complexity from a simple calculating tool to a simulation model with hundreds of input pa-

rameters. These models can also incorporate the extent of uncertainty about specific parameters and explore the potential impact of uncertainties through sensitivity analyses. A projection of the cost-effectiveness of a new personalized medicine could be used to inform manufacturer "go/no go" decisions, particularly if payer and physician acceptance criteria are understood and included in the model. Such approaches are most likely to be valuable in the private sector, where value or return on investment is measured as revenues and profits [52]. From a societal perspective, health benefits may sometimes be approximated on the basis of projected revenue (i.e., market price as a proxy for societal benefit). This assumption, however, may not hold if diagnostics reimbursement is cost-based and not value-based, or if medicine prices and reimbursement are not closely linked to value delivered [48].

HEOR researchers are increasingly using VOI analyses to study the value of research to reduce uncertainties surrounding the benefits, harms, and costs of a health care intervention [53–56]. These

analyses can indicate where the greatest payoff is likely to be in reducing uncertainty about intervention use. VOI analysis can be conducted on the basis of information from preliminary studies, cost-effectiveness models, and informed expert opinion. VOI analyses may be most valuable in the public sector, where quantifying the value of conducting a specific study is more challenging because the information generated is not directly linked to revenues [57].

Early-stage cost-effectiveness analyses models and VOI analyses may be particularly useful in personalized medicine. These approaches can help test manufacturers to prioritize investment decisions, including whether or not to generate more evidence. The same applies to pharmaceutical manufacturers who must decide whether to develop a companion diagnostic that identifies a restricted stratum of patients. These analyses can project the impact of testing on overall efficacy and safety and can also suggest the commercial impact in terms of price, reimbursement, and budget impact—as well as the societal benefits.

### Identification of best practices for clinical evidence development involving PGx

Multiple factors currently complicate the development of clinical evidence supporting diagnostics and PGx, including 1 challenges in early determination of the clinical value of biomarkers; 2 inconsistent understanding or application of diagnostic terminology; 3 variability in diagnostic regulatory requirements; 4 limited incentives to develop "ideal" or direct evidence characterizing test value; and 5 lack of clear and consistent standards for study design or HTA, payer, and provider acceptance [1,58].

Early diagnostic association studies are not often developed to answer downstream decision-maker questions regarding clinical and economic value. Further, the process of regulatory evaluation of tests is more proportionally focused on ensuring standardized processes for testing and test performance than efficacy and safety (unless codeveloped). Some tests may also be subject to stringent evaluation by regulatory bodies, while other tests may emerge as laboratory-developed tests that are subject to very different evidence requirements. These factors often complicate downstream value assessment by HTA agencies, payers, and providers [59].

Whereas therapeutic study designs are generally well agreed upon in terms of acceptability for HTA and reimbursement decision making, this is not the case with diagnostics and PGx studies. Lack of sufficient evidence linking test use to patient management and health outcomes remains a fundamental challenge for reimbursement decisions [37]. There is significant need for identification incentives and harmonization of clinical best practices that reflect specific characteristics of diagnostics and PGx.

Some alternative evaluation frameworks for diagnostics have been proposed in the United States, including by the American Society of Clinical Oncology [60] and the National Institutes of Health [61]. No single approach, however, has yet emerged as standard. These frameworks provide insights into alternative study design approaches that may better address diagnostics evidence questions (e.g., use of retrospective and prospective observational studies). Future HEOR may consider the advantages and limitations of such novel frameworks, as well as differences between stand-alone diagnostics and companion diagnostics validated in the context of phase 3 clinical trials.

Clinical evidence standards and best-practices development for PGx should strive to balance the following: 1 *robustness*: to address HTA and payer questions regarding diagnostic and PGx value, 2 *feasibility*: given current market incentives/limitations, and 3 *flexibility*: including approaches for addressing uncertainties and evidence gaps via alternative study designs or data-collection approaches. Evolving longitudinal data-collection approaches (e.g., real-world data, patient medical records, or registries) should also be explored as alternatives to addressing gaps in clinical evi-
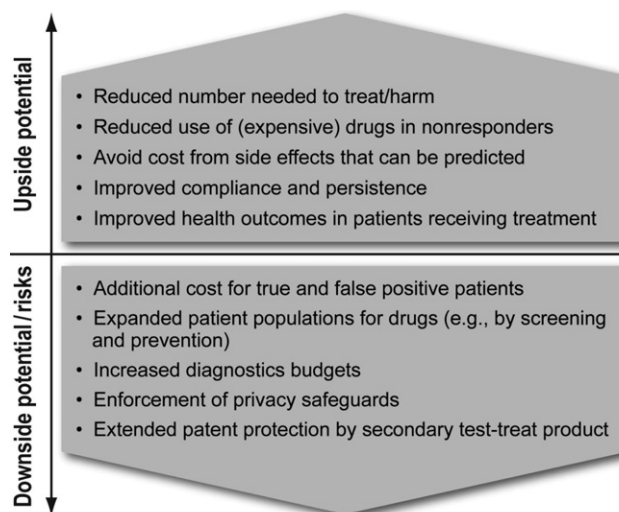


**Fig. 1 – Potential risks and benefits of pharmacogenomics from the payer perspective. Source: Health Outcomes Strategies (2010).**

dence. The implications of time to obtain test results and test reliability should also be considered in the assessment of clinical value. Improving consensus and consistency around evidence development for diagnostics and PGx would in turn support evolution of improved economic assessment in this evolving field.

### Identification of best practices for economic modeling involving PGx

There are well-established scientific standards and key principles for performing economic evaluation and HTA [62–64]. Because evidence from many different types of studies (e.g., test performance, treatment safety and efficacy, quality of life, and costs) must be combined in PGx decision making, decision-analytic modeling may be used to guide such decisions [65]. The special aspects of PGx, however, are not explicitly addressed in the existing guidelines.

As decision-makers and payers show an increased demand for cost-effectiveness data related to test-treatment approaches, there is need for identifying best practices for economic modeling in this field (Fig. 1). This is the case both for codevelopment situations and when the diagnostic is developed as a stand-alone test. In regard to the latter, approaches must address evidence gaps in a manner that is both acceptable to payers and feasible for test manufacturers. Fundamental questions such as how to handle inclusion of the diagnostic in models; characterization of differential budget impact versus SOC; standards for establishing links between test use, patient management, and outcomes; the impact of uncertainty on model outcomes; and whether the QALY is the best metric for diagnostics and PGx remain to be answered [50,66–68]. Model structure, data used as model inputs, and model validation approaches are the three areas in which best practices must be established [69].

Models involving PGx must reflect "real-life" decision making and use. In PGx, the choice to be made is no longer between a new medicine "B" and an existing medicine "A," but between a "treat-all" strategy and a "test-and-treat" strategy. A straightforward way to model this may be to start from the real prevalence of the biomarker that is associated with increased treatment response (or reduced adverse events), as the gene-expression test example in Figure 2 depicts.

As for data input, the rate of false positives and false negatives should be taken into account in the model, as well as consequences of a positive test or a negative test. If evidence on out-
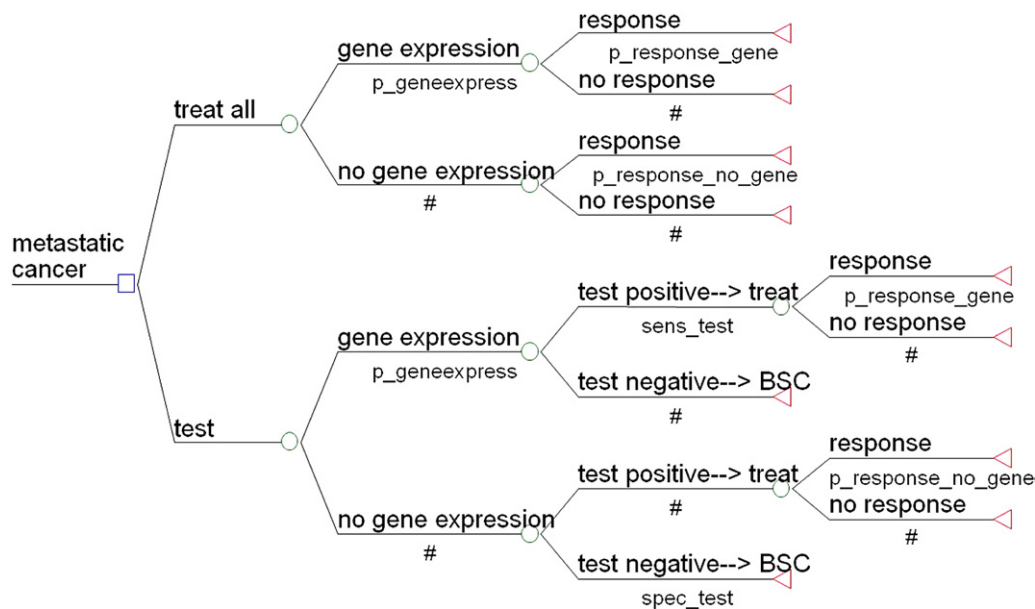
**Fig. 2 – Example of decision tree for modeling economic outcomes of a novel medicine-diagnostic combination. BSC, best supportive care. Source: Health Outcomes Strategies (2010).**

comes is not yet available, the relationship between test results, medical management, and patient outcomes may be assembled from the literature to infer clinical utility. This would be similar to traditional models that translate efficacy into effectiveness. This is particularly true for stand-alone PGx diagnostics that do not follow a codevelopment pathway to yield direct evidence linking test use to treatment outcomes. Extrapolating clinical utility may also be complex for testing scenarios involving multiple biomarkers (e.g., arrays and multiplex tests) that are beginning to emerge in clinical practice, as well as in those cases in which there is a nonbinary outcome of the test. In the latter case, modelers have to consider multiple cutoff points and evaluate together with expert clinicians the medical management and/or further diagnostic practice resulting from the test result [69].

Developing models appropriate for PGx may involve 1 an increased role for expert elicitation methods to populate models and address gaps and 2 increased emphasis on parameter and structural sensitivity analysis to test key assumptions and support decision making. It is also crucial that such models consider approaches to reflect face validity (i.e., the results make sense) and external validity (i.e., the results are generalizable and consistent with real-life data). This is because in the absence of direct clinical evidence, payer scrutiny of modeling assumptions and outcomes will be heightened.

### Addressing HTA challenges for PGx

Although it is possible to use current HTA frameworks to evaluate PGx technologies, there is no evidence to support whether this is either appropriate, in terms of methodological decision frameworks, or feasible, in terms of data requirements. Commonly accepted standards, both within and across different jurisdictions, on how to evaluate diagnostics and test-treatment combinations have not yet been transparently established or agreed upon by leading HTA organizations and payers [11,70,71].

To help ensure that only clinically and economically valuable PGx technologies are used in practice, payers need to develop explicit HTA practices, decision criteria, and utilization metrics [72]. Several organizations such as the European Personalized Medicine Diagnostics Association, the EU Framework VII program, the Eval-

uation of Genomic Applications in Practice and Prevention of the US Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality are working to explore evidentiary criteria for diagnostics and PGx applications. Explicit requirements for health outcomes and economic evidence to support diagnostics are slowly beginning to evolve. Initiatives such as the Technology Appraisal and Diagnostics Assessment Programme of the National Institute for Health and Clinical Excellence in the United Kingdom and draft guidance on assessment of codependent pharmaceutical-diagnostic technologies released by the Medical Services Advisory Committee and the Pharmaceutical Benefits Advisory Committee in Australia are poised to advance economic standards for diagnostics and test-treatment combinations [73,74].

Development of PGX decision analysis frameworks and support tools involving being useful to a broader array of stakeholder decision-makers (e.g., providers and laboratory directors) may also support appropriate adoption and use. Methods for addressing emerging issues such as comparative effectiveness and "real-world" data associated with PGx and diagnostics would also inform the development of necessary best practices [75–77].

As explicit criteria for HTA of diagnostics and PGx evolve, it will be important that such criteria take into account 1 special evidentiary considerations that differ from traditional pharmaceutical/therapeutic scenarios; 2 incentive structure limitations; and 3 different evidence considerations by testing application (e.g., screening, treatment selection, and monitoring) [9,68,71]. Until health system incentive structures that better support the development of diagnostic evidence evolve, clinical and economic methodologies that can help address existing evidence gaps are needed [78]. Recent HTA evaluations, however, have begun to incorporate value considerations specific to diagnostics and PGx, including test performance and the role of diagnostic information in decision making and improved treatment outcomes [79–81].

### Addressing incentive structures and reimbursement for PGx

Various options for companion diagnostic value creation and capture have been analyzed by using a variety of possible scenarios about the sequence of their development and pricing flexibility

[48]. Some health decision-makers have concluded that "value-based, flexible pricing" for both diagnostics and therapeutics could strengthen economic incentives for the development of companion diagnostics and attribution among relevant PGx technologies and stakeholders. Several issues specific to value characterization and HEOR are highlighted as follows.

PGx tests may vary greatly in price as well as in clinical utility. Application of value assumptions to PGx can be challenging because 1 not all tests for a specific biomarker are functionally equivalent or well characterized and 2 multiple test types for a specific biomarker may be available with different levels of supporting evidence. As the field expands, payers will need to find a way to encourage appropriate investigation of the usefulness of PGx while avoiding indiscriminate coverage of tests that may provide limited evidence of value. In addition to evolving payer and HTA processes, some third-party vendors in the United States such as Medco and CVS Caremark are developing processes for managing pharmaceutical access by requiring testing for proven biomarkers. These trends may be supported by adaptive HEOR approaches that link available evidence to appropriate decision frameworks with patient safeguards.

Unlike pharmaceuticals, diagnostics have limited "pricing latitude" and are not typically subject to value-based payment, irrespective of their value to support decision making [9]. Reimbursement of diagnostics is cost-based in most countries and typically results in low prices. There is currently limited ability for the diagnostic manufacturer to gain a return on research and development by capturing some of the value created by a test-pharmaceutical combination. This has in some recent PGx examples led to pharmaceutical company funding the development of the companion diagnostic test itself. To date, the value associated with PGx scenarios (e.g., *HER2* and trastuzumab, *KRAS* and panitumumab, and *EGFR* and gefitinib) has predominantly been captured in the price of the pharmaceutical, creating a dilemma for test developers. Only recently launched multimarker molecular diagnostics (e.g., Genomic Health's Oncotype DX) have achieved value-based pricing via clarifying the likely value of treatment for a particular patient and saving the costs of medicines to payers.

A value-based pricing mechanism will be of even greater importance to PGx test manufacturers associated with generic medicines, such as warfarin, tamoxifen, and carbamazepine. In addition, the scope of patient co-payment and the influence of willingness to pay has at present received limited emphasis in the context of personalized medicine [82].

Nonspecific coding/tariff descriptions that are focused more on describing the process associated with testing (e.g., polymerase chain reaction and fluorescence in situ hybridization) makes it extremely difficult to track outcomes associated with diagnostics. This nonspecific coding frequently requires use of multiple codes (i.e., "code stacking") to cover steps involved in certain molecular testing regimes. This "black box" problem, where payers have limited ability to understand what specific test was conducted, makes it difficult for payers to characterize value and moderate access to medicines. Some groups, such as the American Medical Association, have under way preliminary work on strategies to revamp this nonspecific coding challenge [83].

Another important issue is "Who pays for the companion diagnostic?" and/or "Where will the funding come from to cover the cost of testing?" Recent market access scenarios in Europe and Australia for PGx medicines that require *KRAS* and *EGFR* testing have involved situations where the pharmaceutical manufacturer will pay for testing (either short- or longer-term) as a condition of medicine market access. While this may address some short-term financial pressures, it complicates value characterization for PGx. Implications of this trend will be important to consider for stand-alone diagnostics as such cost-sharing approaches evolve.

It is also important to recognize the limitations of intellectual property protection as a barrier to market entry in the diagnostics arena. Value-based prices will be competed down if test entrants can copy the innovators' approach without having to make the same investment. Low prices and poor intellectual property make it unrealistic for most diagnostic manufacturers to invest in "ideal" studies to demonstrate clinical utility. Currently, therefore, the PGx market is highly dependent on pharmaceutical manufacturers to demonstrate the value of a diagnostic-medicine combination. New incentive models and/or development of HTA models that acknowledge these issues will be necessary to optimally advance PGx.

## Conclusions

This article presents an overview of key issues with PGx applications from the payer and manufacturer perspective, with an emphasis on identifying areas for the development of best practices in personalized medicine. The five broad areas for the development of HEOR approaches specific to PGx (and diagnostics) highlighted here reflect core areas of focus for evolving appropriate best practices and standards, including for clinical and economic evidence development, HTA, reimbursement, and market access for these rapidly evolving technologies.

Although best practices and key principles exist for HEOR and HTA in general, there are no commonly accepted standards for applying these methods to PGx strategies. Development of business incentives and clarification of reimbursement process and payment policy uncertainties represent opportunities for the evolution of HEOR and decision approaches for PGx. Other challenges, such as intellectual property protections, health system infrastructure, and health care reform, also complicate the evolution of best practices and adaptive approaches to addressing PGx.

Many important issues associated with PGx assessment highlighted in this article suggest refinement and adaptation of current HEOR approaches to inform reimbursement and access decisions. This should include evaluation methods that anticipate current evidence limitations. Key areas of refinement include research-prioritization, processes to support business decisions on PGx, re-evaluation of incentive and reimbursement mechanisms, clarification of evidence requirements, and development of decision-analytic modeling approaches that are appropriate for both payers and manufacturers.

While some progress has been made, more research is needed to decide on best practices for PGx, starting from a critical review of current evidence used in HTA decisions for PGx and identification of gaps and challenges relevant to best-practice formation. ISPOR is actively working on the development of adaptive HEOR approaches and standards relevant to the rapidly evolving field of personalized medicine to help address best practices, standards development, and transparent and consistent health decision making.

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