

Pharmacogenomics, Evidence, and the Role of Payers

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Key Words

Evidence-based medicine · Health policy · Insurance coverage · Pharmacogenomics · Reimbursement incentive · Reimbursement mechanisms

Abstract

Initial enthusiasm for the potential of pharmacogenomics (PGx) to transform medical practice has been tempered by the reality that the process of biomarker discovery, validation, and clinical qualification has been disappointingly slow, with a limited number of PGx tests entering the marketplace since the initial publication of the human genome sequence. Reasons for the delays include the complexity of the underlying science as well as clinical, economic, and organizational barriers to the effective delivery of personalized health care. Nevertheless, payers are interested in using PGx services to ensure that drug use is safer and more effective, particularly in the settings of medications that are widely used, have significant risks of serious adverse events, have poor or highly variable drug response, or are very expensive. However, public and private payers have specific evidence requirements for new health care technologies that must be met prior to obtaining favorable coverage and reimbursement status. These evaluation criteria are frequently more rigorous than the current level of evidence required for regulatory approval of new PGx tests or PGx-related drug labeling. To support payer decision-making, researchers will need to measure the impact of PGx testing on clinical and economic outcomes and demonstrate the net benefit of PGx

testing as compared to usual care. By linking payer information needs with the current PGx research agenda, there is the opportunity to develop the data required for informed decision-making. This strategy will increase the likelihood that PGx services will be both reimbursed and used appropriately in clinical practice.

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The underlying premise of pharmacogenomics – that genetics plays an important role in predicting medication response – is scientifically, clinically, and commercially appealing for a wide variety of reasons. Enormous public and financial investments in mapping the human genome have led to a rich scientific literature and numerous experts suggesting that pharmacogenomics (PGx) will be one of the earliest areas of clinical translation for genomic research [1–3]. The process of drug discovery and development has become increasingly expensive [4] and inefficient [5], with fewer new drugs being approved [6] and heightened concerns about the safety of marketed drugs [7]. Again, the promise is that PGx could play a useful role throughout the drug development and marketing lifecycle because of the potential of using genomics to target drug therapies and select patient sub-groups to maximize benefits and minimize harms. The US Food and Drug Administration (FDA) is an active partner in this process of incorporating PGx into drug development; for example the Center for Drug Evaluation and Research has evolved a mechanism for early, voluntary information ex-

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change about pharmacogenomic approaches between drug companies and the FDA [8]. Improvements in biomarker development generally are an area of intense activity under FDA's Critical Path Initiative, which is organizing work across numerous science and regulatory areas to advance product development [9]. The FDA is also creating a guidance document regarding the concurrent development of new drugs and diagnostic tests to guide prescribing decisions [10]. A longer list of inter-agency efforts in pharmacogenomics and public-private partnerships to promote translational research in pharmacogenomics can be found in the recent comprehensive report of the Secretary's Advisory Committee on Genetics, Health, and Society on Pharmacogenomics [11], all signaling the widely shared conviction within the research community that pharmacogenomics will play a pivotal role in realizing the promise of personalized medicine.

Clinicians and patients understand first-hand that drug response is often unpredictable and suboptimal, and there is strong face validity to the hypothesis that some of this variability in treatment outcomes might be explained by genetic differences among individuals [12]. For many chronic disorders, such as psychiatric, neurologic and cardiovascular diseases, diabetes, and cancer, there is a tremendous opportunity to improve response to current medications as well as to develop new targeted therapies that deliver better health outcomes and improve the quality of life of patients. Given the rising costs of health care worldwide and the high costs of drugs in the U.S. in particular, there is growing interest on the part of payers in using PGx as a tool to improve the cost-effectiveness of medication use. The public health benefit of using genomics to improve the risk-benefit profile of new and existing drugs, while ensuring efficient use of scarce health care resources, is potentially enormous. All of these enabling forces to promote the use of PGx in clinical practice undoubtedly have contributed to the extensive, generally favorable media coverage of this new technology that often gives the impression that PGx is more mainstream than is the current reality [13–15].

Given the ongoing need to improve the effectiveness and efficiency of medication management and the presumed benefits of PGx testing, payers are tracking developments in pharmacogenomics with increasing intensity. Today, most payers in the U.S. apply their standard procedures for evaluating new health care technologies to PGx tests, while trying to determine what (if anything) about this particular type of biomarker assay might require specialized review. The purpose of this paper is to

describe the decision-making framework for coverage decisions in the U.S., primarily to make the case that lack of evidence of clinical benefit is one of the most important barriers to clinical integration of PGx testing. Specific examples of U.S.-based private insurer coverage decisions regarding PGx tests will be provided, with particular emphasis on cancer, as oncology is an area of early application for PGx testing. Most importantly, since better information about the incremental benefits, risks, and costs of using genotypic data to help guide prescribing decisions (compared to usual care) represents the critical translational hurdle for the field of pharmacogenomics, the paper will review a series of policy solutions that have been proposed as potential strategies for closing the evidence gaps.

Current State of PGx Testing

Today, a growing list of drugs have some type of reference to PGx included in their labeling [16], either for germline mutations (e.g., cytochrome P450 drug metabolizing enzyme variations) or for somatic mutations (e.g., *HER-2/NEU* overexpression in breast cancer tissue). A few drugs (trastuzumab, maraviroc) have been co-developed with a PGx test used to create an enriched, pharmacogenomically defined clinical trial population, and for these drugs PGx testing prior to prescribing is required. However, the vast majority of these labels simply refer to a reported PGx association (e.g., alteration in drug metabolism or drug interactions) and do not specifically recommend or require testing prior to prescribing a drug [17]. While certainly an important initial step for the field of pharmacogenomics, there currently is a lack of prospective evidence linking PGx testing and changes in drug management, and there is much uncertainty about how to incorporate PGx labeling information into clinical practice [18, 19]. The regulation of genetic tests (both disease predisposition and PGx tests) has been an area of intense debate and will not be reviewed here [20]. Suffice it to say that whether a PGx test reaches the marketplace in the U.S. either through the laboratory-developed test pathway or via FDA approval, there are no regulatory requirements for developers to provide evidence of clinical validity or clinical utility; the evidence standards for these criteria become the purview of clinicians and payers [21].

Many reasons have been cited for this gap between the promising science of pharmacogenomics and the translation of a useful PGx test into clinical practice, such as the

regulatory structure for laboratory tests, the reimbursement system, and the prevailing business and development models within the diagnostics industry [22, 23]. The recent report on pharmacogenomics from the Secretary's Advisory Committee on Genetics Health and Society analyzed the translational barriers from the perspectives of the various stakeholder groups such as industry, FDA, CMS (Centers for Medicare and Medicaid Services), and other 3rd party payers and clinical practice guideline developers and came to the same general conclusions with respect to the role of payers [11]. This group plays a critical gatekeeper role in deciding which PGx tests are readily accessible to patients and clinicians and increasingly uses evidence of clinical utility as the basis of this decision. The term clinical utility has been defined quite broadly, to not only include the impact of the PGx test in routine practice on patient health outcomes, but to also include the ability of testing to inform clinical decision-making while accounting for availability of resources and patient preferences and moral values [11, 24]. Payers typically want to sanction the use of PGx tests that have demonstrated analytic and clinical validity (characteristics of the test and the prevalence of the genetic variant in the population), but most importantly lead to appropriate clinical decisions and actions that result in net health benefits for patients.

Role of Payers

Rising health care costs continue to be a central challenge for most governments, with aging populations and health care systems based primarily on high tech western medicine. At the current rate of increase, health care spending in the U.S. will consume 20% of gross domestic product (GDP) by the year 2016, with approximately equal shares financed through the public and private sectors [25]. Payers want to know if consumers are receiving better health or even just better health care in return for this enormous investment and have attempted to use their purchasing power to promote value for money in medical care. To fairly assess value requires a comprehensive evaluation of both the comparative effectiveness of a new medical technology (e.g., a PGx test) as well as the relative costs of that new technology. There also needs to be reliable evidence of effectiveness of PGx testing in 'real world' patient groups, practice guidelines to facilitate changes in clinical management, and laboratory test reports that can be utilized by clinicians without subspecialty training in genetics (table 1). The concept of testing

Table 1. Payer information needs

Well-designed, well-conducted studies demonstrating impact of PGx testing on:
(a) clinical outcomes (effectiveness; safety)
(b) economic outcomes (direct and indirect costs; budget impact)
Studies comparing PGx testing to usual care (prospective; ideally randomized controlled trials)
Studies conducted in real-world populations
Studies published in peer-reviewed literature
Algorithms or clinical practice guidelines to guide appropriate use of test in clinical practice including need for informed consent, referral for genetic counseling
Education for clinicians and patients

Semi-structured interviews conducted with 9 payers and 8 health care delivery organizations [see reference 56].

a patient prior to prescribing a drug to optimize the selection of a particular drug or dosage in order to increase the likelihood of response and decrease the risk of adverse reactions is appealing to payers, but they need to also consider the cost of the PGx test and how the test will be used in clinical practice. For example, PGx testing is likely to be economically feasible only in well-defined clinical circumstances, such as for drugs with a narrow therapeutic index, with highly variable response rates, and where there are limitations for monitoring adverse drug reactions [26]. Similar criteria would be used to predict the likely public health impact of a new PGx test.

The trend in the payer community is to demand robust evidence of the impact of a new technology on clinical and economic outcomes, preferably compared to an appropriate real-world alternative intervention in a prospective study. This same framework for coverage decision-making and similar evaluation criteria will be used by payers for PGx tests as they would be for any other innovative technology – namely evidence of clinical utility (risks and benefits of using PGx testing in clinical practice) and, to a lesser degree, cost-effectiveness. (Essential parameters such as evidence of analytic and clinical validity that are somewhat specific to diagnostic tests must also be present before an assessment of clinical utility is meaningful) [20]. The persistent dilemma for diagnostic tests is that the published literature is generally inadequate for the purpose of evaluating clinical outcomes and conducting systematic evidence reviews [27]. In an effort to improve the evidence base for diagnostic tests and to facilitate informed decision-making by payers, a frame-

work for presenting the evidence on laboratory tests that could be applied to PGx tests was developed based on an approach that has been successfully used with many U.S. payers for the evaluation of new drugs [28]. While useful in defining the information needs of payers, very few PGx tests have met this evidence hurdle.

Coverage Policy

While the terms ‘reimbursement’ and ‘coverage’ are sometimes used interchangeably, coverage specifically refers to the scope of services a payer will pay for and under what circumstances, while reimbursement refers to the level of payment. Coverage policy has typically focused on reimbursing for services within contractually defined categories or for services viewed as ‘medically necessary,’ although the determination of medical necessity has often been controversial, and more recently some large payers are applying evidence-based approaches to coverage decision-making [29]. In addition to explicit definitions of covered services and the concept of medical necessity, payers also consider whether they will classify a PGx test as experimental/investigational, a category that is typically excluded from coverage [30]. The overall impact is that without a favorable coverage policy, the test will not be reimbursed, and most patients will not have access to the new technology. This is a major reason that payers have shifted to the principles and practices of evidence-based medicine, as they attempt to balance improving quality of care and cost-containment through appropriate access to effective interventions.

Reimbursement levels for molecular diagnostic tests are currently governed by the CMS Clinical Laboratory Fee Schedule in an antiquated system of ‘cross-walking’ or matching new tests to existing tests based on features related to apparent technical comparability [31]. This system has led to significant under-reimbursement for most PGx tests, which can make product innovation more unlikely if companies or their investors believe that they will not realize a reasonable return on their investment in research and development costs. Similarly, reimbursement rates that are set too low make it economically difficult for laboratories to offer PGx testing because of a financial loss [32]. The net result of this financial uncertainty is that most small PGx-focused companies cannot afford to conduct the type of prospective outcomes studies to demonstrate the value that they believe their new test will deliver.

Table 2. Blue Cross Blue Shield Technology Evaluation Center criteria

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- The technology must have final approval from the appropriate governmental bodies
 - The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes
 - The technology must improve the net health outcome
 - The technology must be as beneficial as any established alternatives
 - The improvement must be attainable outside the investigational settings
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<http://www.bcbs.com/blueresources/tec/tec-criteria.html>.

Technology Assessments

Large payers such as Medicare or Blue Cross Blue Shield (BCBS) often rely on separate technology assessment panels to evaluate the evidence supporting the use of a new health care technology. These panels use explicit criteria and the best available scientific evidence to determine whether a new technology improves patient health outcomes and publish their findings in reports that are utilized for coverage decision-making [29]. The BCBS Technology Evaluation Center (TEC) program has one of the best-established processes for systematic clinical evidence reviews (table 2) and conducts 20–25 technology assessments per year. Interestingly, pharmacogenomic testing has been an area of high activity in the past several years. For example, the TEC program has published evidence reports for genotyping of *CYP2D6* polymorphisms for tamoxifen and to determine drug-metabolizer status, PGx-based treatment of *Helicobacter pylori* infection, gene expression profiling of breast cancer to select women for adjuvant chemotherapy, and epidermal growth factor receptor mutations in advanced non-small cell lung cancer. Acknowledging that FDA approval is not required for PGx tests regulated as laboratory developed tests and conducted in a CLIA-certified laboratory in the U.S. [33], TEC found evidence of clinical utility to be lacking for all PGx tests they evaluated with the exception of the Oncotype DX test for breast cancer. The absence of prospective studies demonstrating an improvement in health outcome relative to usual care (patients managed on drug therapy without PGx testing) was the major reason that the report findings were overwhelmingly negative. A similar conclusion has been reached by the CDC’s EGAPP committee in their evaluation of *CYP450* testing [34]. The EGAPP report on using gene expression profil-

ing to impact breast cancer outcomes found that there was preliminary evidence of clinical utility for only one (Oncotype DX) of the 3 tests currently on the market [35].

While the TEC assessments are silent about whether the new technology (e.g., the PGx test) should be covered, these reports are used by local BCBS plans as well as other insurers to inform their own internal coverage decision-making processes. The coverage decisions of many health plans and insurers are considered proprietary, but some companies, such as Aetna, make their coverage decisions public [36]. Their process is noteworthy not only because they are using a systematic, evidence-based approach as justification for their assessment of medical necessity, but also to emphasize the disconnection between the levels of evidence to gain marketplace approval versus a favorable coverage decision. In multiple cases (e.g., tests for *CYP450* polymorphisms, *UGT1A1*, and *VKORC1*), the payer may still conclude their use is experimental and investigational because of a lack of evidence establishing the clinical value of the test. Other private insurers have conducted their own technology assessments for PGx tests, but the process is not standardized and the evidence base for coverage decision-making is not known [30].

Value-Based Purchasing

Value-based purchasing seeks to use reimbursement to support the use of effective health care interventions and avoid payment for ineffective care. However, this strategy is directly dependent on the quantity and quality of evidence available for coverage decision-making. Questions such as whether PGx testing will be of value and how that value should be defined and measured have been widely debated in the literature. One well-established approach for determining value is to assess both costs and outcomes and the economic framework that has been most commonly applied to PGx tests in cost-effectiveness analyses [37]. There have been a relatively few published cost-effectiveness analyses of PGx interventions, with a large opportunity to improve the existing evidence base [38]. Although there are gaps for many critical data inputs, such as the incidence of adverse drug reactions and their associated costs, one of the biggest missing pieces is the relationship between PGx testing and clinical outcome. For example, when the authors hypothetically analyzed *CYP2D6* testing in terms of the data elements that would be used in a cost-effectiveness analysis, they found that only one-third of the drugs that

were both metabolized by *CYP2D6* and were associated with high costs/high utilization had data on clinical outcomes [37]. Ideally one would want data regarding the associations for metabolism, drug response, and clinical outcomes; no drug has this level of evidence. Until we conduct studies to establish the relationship between genetic variation and clinically relevant outcomes, any cost-effectiveness analyses are severely limited in their ability to inform payer decision-making.

Cancer – an Early Case Example

Payers often equate pharmacogenomics with expensive biotechnology drugs because one of the earliest and best examples of PGx testing is *HER-2/NEU* testing for herceptin. However, they remain particularly interested in using PGx testing to help manage the rapidly increasing biotechnology-drug spending as well as to improve medication-related health outcomes [39]. Oncology is an area of intense research activity in pharmacogenomics, and tumor genotyping has revealed the complexity of cancer and the opportunities for tailoring treatments to individual patients. Some of the best examples of the early progress in PGx testing have been in the area of genetic testing for somatic mutations in breast and lung cancer.

Experts are predicting that optimum treatment is likely to consist of a ‘cocktail’ of different inhibitors based on the genetic profile of a particular tumor [40]. Payers are concerned because they see the reality of treatment ‘stacking’ where several different expensive new biologics are now given in combination, typically off-label, without good evidence that this novel combination therapy will appreciably extend the quality and quantity of the patient’s life [41]. Even when a new PGx test such as Genomic Health’s Oncotype DX has been shown to be useful in helping oncologists decide which patients with breast cancer are most likely to benefit from chemotherapy, there still may be additional marketplace hurdles. For example, UnitedHealthcare, one of the largest insurers in the U.S., made the decision to cover Oncotype DX, but they will not pay for the test in the situation where an individual with a low risk score goes on to receive chemotherapy anyway (low scores indicate low risk of breast cancer recurrence and therefore no need for adjuvant chemotherapy). The rationale offered by United’s chief medical officer, Lee Newcomer, is that ‘there is no reason to do the test or have an insurer pay for it if the doctor doesn’t take its advice,’ and suggests heightened scrutiny

for the test because of its novelty and cost [42]. Despite reimbursement rates in the 3,500 USD range, Genomic Health (Redwood City, Calif., USA) states that it has yet to see a return on its investment, primarily because of the financial outlays made by the company to conduct studies to demonstrate the clinical utility of the test. Whether the Genomic Health example will become the norm for evidence development or represents a high water mark is not clear at this time; however, there are real concerns that most diagnostic companies will not be able to replicate their approach because the studies are too difficult and too costly [42, 43].

Potential Solutions

The problem of lack of comparative effectiveness data is a problem that affects most innovative medical technologies and is certainly not a new problem for the U.S. health care system [25]. There are several policy recommendations for this systemic issue that can be applied to pharmacogenomics. These strategies fall into 2 broad categories: private or public subsidies for research on comparative effectiveness or the creation of incentives that encourage market-based approaches for evidence generation. For example, the government can directly fund this type of research. Although currently only a very small amount of the federal research budget in the U.S. is spent on health services research compared to basic or clinical research [44], there is a growing recognition of the potential benefits of more centralized and systematic comparative effectiveness research, particularly as the results may be applied to technology dissemination efforts [25]. Additional funding could be provided to existing federal agencies such as the Agency for Healthcare Research and Quality (AHRQ) that already conduct health services research, or there are potential advantages to the proposals for the creation of a quasi-governmental entity like the Institute of Medicine [45] or a public-private partnership such as the Transportation Research Board of the National Academies [46].

Financial support could also come from the private sector through a variety of mechanisms, such as voluntary contributions (potentially undesirable as it may encourage ‘free riders’) or charging a fee on all users of the information (e.g., payers, providers) [45]. Since payers as a stakeholder group have a particular need for information regarding which treatments work best, there has even been a proposal from the Blue Cross Blue Shield Association (BCBSA) to create a solely payer-funded insti-

tute to conduct a broad range of studies, including much-needed clinical trials. Recognizing that public and private payers would directly benefit from this research and that the absence of a large and stable funding source was a critical barrier, the BCBSA proposed that payers move forward as a group to act in their long-term self-interest [47]. There are ongoing efforts to pass federal legislation to create a comparative effectiveness institute within AHRQ or NIH, but a final resolution is unlikely until after the 2008 presidential election in the U.S., and contentious issues such as oversight, levels of funding, and political opposition are addressed in a manner that balances the concerns of the various stakeholder groups.

The 2nd category of strategies to promote evidence generation emphasizes the importance of financial incentives such as research tax credits and higher reimbursement rates for innovative products introduced to the marketplace with better clinical utility data. There could also be legislative remedies to encourage the conduct of prospective outcomes studies for PGx tests specifically by the private sector. For example, the Genomics and Personalized Medicine Act of 2006, introduced by Senator Barak Obama, included the concept of a research tax credit for companies that sponsor the appropriate outcome studies. The bill was reintroduced in the 110th Congress by Senators Obama and Richard Burr with only a proposal for a study to be conducted to recommend a series of incentives to expand and accelerate genomics research. The latest version of the bill [48] introduced by Representative Patrick Kennedy (Genomics and Personalized Medicine Act of 2008) revived the concept of tax incentives for genomics research and signals a high-level recognition of the barriers to evidence generation that exist in the current system. A tangential legislative remedy would be to change the Medicare prevention exemption language that would potentially exclude coverage of PGx testing. While CMS has not issued a formal position regarding coverage of PGx testing, ongoing concerns regarding the current enabling legislation that excludes payment for any services that are determined to be preventive represent a disincentive for industry to develop PGx tests for the Medicare population [49].

In the near-term, changes to the reimbursement environment could be the most direct way to generate the desired evidence of effectiveness. This is why there has been a growing recognition of the need to permit provisional coverage for new technologies while simultaneously requiring collection of additional evidence of effectiveness post-marketing, such as CMS coverage with evidence development policy [50]. Based on feedback from various

stakeholders, CMS revised its original coverage with evidence development policy, yet still provided a process for linking provisional coverage for promising technologies to the requirement for patient participation in a registry or clinical trial. The goal was to create a process that provides access to innovative technologies, while simultaneously requiring companies to generate the evidence CMS needs to make more informed, evidence-based coverage decisions. Experience so far has been limited; to date the process has only been applied to a small number of contentious procedures and biologics where the data supporting their use in the Medicare population fell below the evidence standard for unlimited coverage [51]. Other experts have suggested a two-track system that rewards innovators (primarily in the form of higher reimbursement rates) who conduct long-term outcome studies for products that are initially approved for clinical use on the basis of biomarkers and short-term outcomes [52]. Specifically for PGx tests, strong intellectual property protections and flexible, value-based pricing schemes have been singled out as 2 critical improvements to the current system that need to occur before developers will have the proper incentives to fund the research needed to improve clinical adoption [53]. However, patent protections for diagnostics may be less durable than for drugs and therefore still not be sufficient to stimulate optimal levels of evidence generation for PGx tests.

The application of pharmacogenomics to improve the safety and effectiveness of warfarin therapy has been an area of intense research activity because of the high unmet clinical need for optimizing oral anticoagulation and the growing body of evidence that genetics plays a role in explaining the variation in international normalized ratio (INR) response [54]. While there are a number of ongoing clinical trials that will address many of the remaining clinical questions about genomics guided warfarin therapy, there are 2 interesting examples of how the payer perspective has influenced the conduct of research in this area. First, the pharmacy benefit manager (PBM) Medco has partnered with the Mayo Clinic to evaluate the impact of PGx testing on patient safety and medical costs in 1,000 patients prescribed warfarin. The study takes advantage of Medco's access to large numbers of patients in its role as a PBM and clinical experience with patient safety programs and is unique because the study is conducted in community-based settings and includes the measurement of costs. The collaboration with the Mayo Clinic allows the communication of genetic test results directly to the prescribing physician for use in determining the appropriate dose of warfarin [55]. Second,

the Institute for Pharmacogenomics and Individualized Therapy at the University of North Carolina has designed a pragmatic clinical trial of PGx-guided warfarin therapy that has chosen a reduction in the number of outpatient visits as the primary endpoint of the study. After consulting with payers, policy makers, clinicians, and regulators, the investigators decided to pursue an economic endpoint as the primary outcome measure to address unanswered questions about the efficiency of genomics-guided treatment relative to usual care. This is in contrast to most other clinical trials of genomics-guided warfarin therapy that have focused on the amount of time spent in therapeutic range during the 1st month of therapy as the primary endpoint. Results from these 2 studies will add important, complementary information to the growing body of evidence about the clinical utility and cost-effectiveness of PGx-testing and are promising illustrations of how the evidence gaps can be addressed by collaborative research efforts.

Conclusions

While the regulatory environment is a powerful influencer of whether and how PGx tests are developed, the mechanisms by which PGx services are covered and reimbursed are ultimately the final determinants of whether most patients will have access to PGx tests. Payer decision-making is of course influenced by the degree of clinical impact a new PGx test will have in the target population, but increasingly the case must be made based on strong scientific evidence of clinical utility. In the U.S., test developers face a decentralized network of public and private payers, each with their own criteria for evaluating new health care technologies, although the trend is for each organization to follow a process that systematically evaluates the best available evidence in light of existing coverage criteria. Perhaps not surprisingly, payers are utilizing the same assessment criteria for PGx testing that they would use to evaluate any other innovative technology [56]. What is problematic about this approach is that most diagnostic companies developing PGx tests currently lack the appropriate incentives and research infrastructure to conduct the types of prospective studies required to demonstrate evidence of clinical utility and (ideally) cost-effectiveness. Similarly, most federally funded studies conducted by academic institutions also fail to answer the questions of greatest clinical and economic interest to payers – the types of questions typically addressed by health services research. This situ-

Table 3. Payers' role in clinical integration of PGx tests

Conduct technology assessments
(a) define outcomes of interest (e.g., clinical utility, value)
(b) determine evidence base
Make coverage decisions
(a) determine medical necessity
(b) determine experimental/investigational status
Strongly influence patient access
Shape provider behavior
Affect innovation
Participate in research collaborations

ation can be improved over time by implementing a series of policy changes, some of which are being recommended as part of health research reform efforts more generally, others that specifically address the unique translational barriers for PGx tests [11]. To the extent that the evaluation of PGx tests can 'ride the wave' of growing support for improvements in every type of research to increase the use of effective medical interventions, there should be predictable improvements in public health. In the meantime, it is critically important for researchers and developers to become more aware of the information needs and evaluation criteria of payers and technology assessment panels (tables 1 and 2) and the role they play in determining access to new PGx tests. By connecting the 2 ends of the translational spectrum, there will be a greater likelihood that studies will be designed to meet the infor-

mation needs of payers. This will set up a series of positive conditions for PGx tests, including a favorable climate for investment, increased test access for patients, and increased test adoption by clinicians (table 3). Payers may also play an active role in research efforts by collaborating in study designs, patient recruitment, study dissemination, or funding initiatives as we have already begun to see in some of the innovative studies being conducted for warfarin. While there are many factors that impact the translation of PGx tests into clinical practice, this paper has emphasized the role of evidence in influencing payer decision-making. Certainly, evidence alone is insufficient to ensure appropriate use of PGx testing in clinical practice, but without good evidence it is difficult to make rational coverage decisions and equally difficult to translate research findings into specific treatment recommendations that can be interpreted by practicing clinicians. We are beginning to see more private-public collaborations and innovative approaches to help redesign the research enterprise to improve the evidence base for PGx tests. This will require that we have the appropriate reimbursement structure in place to reward developers of PGx tests that demonstrate value to the health care system.

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