A New Model for Reimbursing Genome-Based Cancer Care

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The rapidly increasing number of targeted agents, biomarkers, and molecular diagnostics has greatly increased the complexity of cancer diagnosis, prognosis, and treatment. The U.S. Food and Drug Administration (FDA) lists nearly 40 indications for which molecular testing is used in oncology [1]. Several manufacturers are marketing single and multigene assays to predict outcomes, either to general treatments or specific agents. Perhaps more important, next-generation sequencing technologies, which are currently available at most comprehensive cancer centers, may soon enable inexpensive assessments of genomic disruptions in patients' tumors on a wide scale. The ability of cancer care facilities to perform complete or near-complete assessments of tumor genes and gene products "in house," combined with the U.S. Supreme Court's unanimous ruling that human DNA sequences cannot be patented (*Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 US, 12-398 [2013] [2]), may be disruptive to the emerging genomic testing industry because centers owning sequencing technologies can reproduce proprietary assays. Perhaps more important for clinicians is the possibility that the information provided by sequencing, combined with the growing literature cataloging how these disruptions affect the biological function of the cancer cells across tumor types, may lead to a time when cancer therapy will be defined not only by the site of the cancer (e.g., breast or lung) but also by matching the patient's aberrant genomic morphology to one or more drugs that have been shown to be effective in targeting those disruptions in those tumors [3]. A roadmap has already outlined the process by which oncology will move from the current model of patients being managed through well-defined and referenced therapy "pathways" to highly variable individualized combinations of treatments that are based on a genomic signature specific to the patient's tumor [4].

Although holding tremendous promise, molecularly targeted medicine poses serious challenges to clinicians and payers. For clinicians, the challenge is in knowing when to apply these technologies to patients. For payers, the difficulty is determining when to pay (or not) for the tests and associated treatments. Inexpensive genomic sequencing, combined with laws (in most states) that mandate reimbursement for off-label uses of oncology drugs, creates a potentially problematic scenario in which drugs are prescribed based on targets rather than on evidence that "treating the target" is beneficial. Evidence is emerging that tumor responses to targeted agents

are very context specific. BRAF inhibitors, for example, appear to have activity in melanoma and thyroid cancer with the associated variants but not in colorectal cancer [5–7]. We believe that this "evidence problem" in pharmacogenomics, combined with the very high cost of targeted drugs, will lead payers to develop radically different coverage policies for companion genomic tests and cancer drugs. The new policies will need to balance clinical flexibility in tailoring therapies against the need to ensure that patients are guided to cost-effective strategies. We assert that performance-based risk-sharing arrangements (PBRsAs) may be a promising approach to address these competing needs.

ENVISIONING A GENOME-DRIVEN PRACTICE

In practice, the new era of targeted therapy is likely to work in one of two ways. The first approach involves initial therapy selection based on known mutations and prospective and retrospective data on prior patients with similar genomic profiles whose outcomes are known (genome-backward medicine) [4]. For patients who have failed conventional therapies or for whom there are no clearly delineated guidelines on therapy choice, new therapeutic strategies could be attempted based on the comprehensive analysis of the tumor's genetic signature (genome-forward medicine). The widely cited BATTLE trial for patients with chemorefractory lung cancer is an example of this approach [8]. Companies have been developed to facilitate both genome-forward and genome-backward processes [9].

Disruptive as in-facility whole-genome sequencing may be for the diagnostics industry, it is unlikely to be a major factor for health insurers as long as price parity between commercial tests and in-facility tests is maintained and cancer care facility laboratories running these assays maintain Clinical Laboratory Improvement Amendments certification. The Center for Medicare and Medicaid Services currently uses a crosswalking method to set payment rates for new tests based on existing tests that use comparable technologies or gap filling to set fees for new tests that have no clear antecedent. In addition, targeted-therapy treatment decisions also are unlikely to create issues, particularly if the decisions are based on guidelines, compendia, or evidence-based pathways. Health insurers will have problems with genome-forward approaches when choices are made based on mutational signatures but where evidence supporting the use of targeted therapies in

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the particular clinical situation is insufficient or lacking. In this case, how can clinicians move forward with a management approach that is essentially ad hoc but supported by biological rationale?

The traditional insurance policy tool to limit use of high-cost drugs is “prior approval” or “prior authorization.” Most oncologists are familiar with these programs: before granting coverage, the prescribing doctor must provide information to the insurer or pharmacy benefit manager about the clinical indication and rationale for prescribing the medication of interest. Prior authorization is relatively easy to administer for health plans and clinicians (although few clinicians have favorable opinions of the process) because it follows clinical practice guidelines and labeled or approved off-label uses that are supported by evidence. In the case of whole-genome-guided therapy, however, there might not be a reference guideline or evidence supporting the strategy. In this case, prior authorization is of little use.

PERFORMANCE-BASED RISK-SHARING AGREEMENTS: A WAY FORWARD?

Performance-based risk-sharing arrangements are a contract between a payer and a product developer where the price level, reimbursement, or revenue received is linked to the future performance of the product [10]. These arrangements reduce the financial risk to the payer while additional evidence is gathered to support a final coverage decision. Two research groups have published detailed taxonomies and assessments of these arrangements [5, 11]. More recently, an International Society for Pharmacoeconomics and Outcomes Research task force on PBRsAs has defined two general types of arrangements: (a) reimbursement is linked to product performance in the real world, and (b) limited access is provided with a plan to collect and evaluate additional evidence (e.g., coverage with evidence development) [12]. The goal of these arrangements is to allow limited access to promising but unproven technology while additional evidence to support broader access is gathered.

PBRsAs are traditionally established between the product developer and a payer based on evidence generated for a single technology in a specific clinical setting. For example, the developer of bortezomib (a product to treat multiple myeloma) agreed to an arrangement with the U.K. National Health Service that links payment to tumor response measured using serum M protein [13]. Such two-party arrangements simplify contracting and allow payments to be structured efficiently. For tailored cancer therapy, however, multiple parties could potentially be involved (e.g., payer, product developer, testing facility, and prescribing facility). In the U.S., the testing and prescribing facility may be the same, particularly for large cancer centers. Including multiple groups will create contracting challenges, raise transaction costs, and add a layer of uncertainty when apportioning financial risk.

A fundamental issue for PBRsAs regarding care driven by whole-genome sequencing is identifying parties who will share the risk. In this case, we suggest that the risk-sharing arrangement be between the payer and the cancer care facility or provider group. This is quite different from traditional models between payers and developers. The primary reason we advocate for payer-facility PBRsAs is that transaction costs

can be minimized under this arrangement, particularly if both groups set up a process that apportions risk based on one of the methods described above. In clinical terms, the expected complexity of practicing genome-directed therapy (multiple possible therapy combinations based on a genomic variant signature) could not be managed by drug developers as part of a traditional risk-sharing arrangement. Instead, health systems providing care could set up agreements with payers based on clinical outcomes that both could monitor, leaving providers with the freedom to make individual treatment choices.

We offer an example of one possible scenario: the “Master Protocol,” a template approach to genomically driven clinical trials using existing and experimental targeted therapies that is sponsored by the North American Cooperative Clinical Trials Groups, Friends of Cancer Research, the FDA, and the National Cancer Institute [14, 15]. The initial master protocol focuses on second-line therapy for patients with squamous cell-type non-small cell lung cancer. In this study, patient tumors are genomically screened and then randomly assigned either a treatment based on markers found on screening or standard care. Patients are then followed for progression and overall survival.

An arrangement similar to the Master Protocol could be replicated in community practice for currently approved targeted drugs. A cancer center and health insurer, for example, could agree to a risk-sharing strategy for patients with advanced non-small cell lung cancer who show progression after standard first-line therapy following established guidelines. Rather than paying only for standard second-line agents or regimens, under the performance-based risk-sharing agreement, the insurer agrees to cover a strategy that is based on full genome sequencing (this includes the price of the sequencing itself) and off-label use of drugs that have shown some promise in early evaluations. The agreement includes performance metrics that are established beforehand, for example, that survival will be equal to median survival observed in clinical trials of second-line agents. Other outcomes such as tumor response or toxicity also could be chosen. Providers and patients would then be free to choose treatments based on the genomic profile of the tumor. The proportion of the facility’s bills that would be reimbursed for that patient would be based on whether the prespecified metric is met (e.g., patient survives 5 months from start of second-line therapy). The provider, the cancer care facility, and the payer agree to data-sharing arrangements with the potential to track the prespecified metrics. In cases that would require measurement of outcomes from the electronic medical record (which are not typically available to insurers), the treating facility or provider group would set up an arrangement for sharing data either with the insurer or a neutral third party that could maintain privacy and ensure that the agreement was adjudicated fairly. Processes would need to be in place to make sure the data are collected with high standards and are periodically audited by independent third parties to assess quality and completeness.

Although this model allows providers to provide cutting-edge genomically driven care, it also introduces constraints to ensure that the treatments are not simplistically chosen based on a genomic signature. If such a choice were made and the outcomes were below standard care, the provider would be

responsible for the cost of the tests, the drugs, and the associated care.

PROTECTING CANCER CARE FACILITIES AND PROVIDERS FROM EXCESS RISK EXPOSURE

In general, the type of PBRSA we describe could be applied only in settings where cancer care facilities and providers could bear the risk of short-term losses. PBRsAs also imply a reasonably sophisticated information technology system that can link clinical information with expenditure data so that patient treatments, outcomes, and costs can be monitored and managed simultaneously. Systems for linking treatment, response, survival, and costs are routinely used for clinical trials and are in place at most major cancer centers, but few community-based systems have this capacity today. It is reasonable to ask whether cancer facilities would invest in such a system, given the uncertainties that currently exist for whole-genome-guided therapy. In reality, contracts would probably need to err toward protecting cancer care facilities and providers in the short run and be limited to a relatively few regional groups so that outcomes and costs could be monitored closely. In return, it would be reasonable for insurers to demand a higher level of data sharing periodically so that they can learn from the experience and design more equitable contracts in the future. In practice, it is likely that some centers would withdraw because the arrangement would prove too costly or cumbersome.

DATA COLLECTION AND DISSEMINATION

A requirement for a successful PBRSA is information. Programs for data collection and sharing are critical. Health insurance claims alone are unlikely to provide the clinical detail that would be necessary to determine whether the patient is eligible for a genomically based therapy plan or to capture measures of outcomes that would be sufficient to determine whether performance metrics were met. In this case, the treating facilities would likely need to provide the bulk of the information to the payers. At a minimum, we believe the information sharing should contain the following items: (a) clinical indication (e.g., cancer type and stage, previous therapies applied); (b) genomic sequencing technology used; (c) treatments applied (including supportive care medicines); (d) prespecified adverse outcomes that constitute clinically significant events (e.g., febrile neutropenia, cardiovascular events, nausea or vomiting requiring hospital admission); and (e) measures of therapeutic success that can be compared with clinical endpoints that are reported for alternative strategies. Although this list may seem onerous to some providers, it is important to note that PRBSAs would supplant the current prior authorization process, that is, day-to-day decisions would not be encumbered by having to notify insurers and gain approval for specific drugs or regimens.

Because collection and reporting of these clinical endpoints may be costly, it may be necessary for all stakeholders to contribute funds to an infrastructure for reporting. Although some payers might argue that the burden of providing performance metrics lies solely with the care facility and the provider, it has been noted that there are “public good” aspects

to the information provided in PBRSA [7, 16], particularly because the information connecting genetic signatures, targeted therapies, and outcomes would be highly valuable for medical research.

CONCLUSION

The U.S. health care system is in the midst of rapid and wide-ranging payment reform. Risk-sharing arrangements represent an innovative reimbursement model in which both the supplier and the payer have a stake in patient outcome. In cases where cancer care facility and payer PBRsAs are established, it will be important during the process of discussing treatment options to share with patients the fact that these contracts exist. Because contracts could theoretically include limits on total reimbursements or restrictions on particular types of care, patients would need to be told of these issues so they could make informed choices regarding whether to choose a genomically driven therapy versus an alternative. Because of the potentially complicated nature of PRBSAs, patients with low socioeconomic status may require third parties to advocate with providers on the patient’s behalf. This may be an appropriate role for cancer advocacy organizations (e.g., American Cancer Society), given their access to clinical information as well as their depth of knowledge of the cancer care delivery system.

There is concern that PRBSAs between insurers and product developers could negatively influence innovation [17]. This is not likely to be true for facility-payer PRBSAs in whole-genome sequencing-guided care. In fact, lessons learned from these arrangements are likely to accelerate knowledge about the use of targeted agents in a wide variety of cancers, provided that data can be pooled across cancers and/or cancer variant signatures.

To our knowledge, PRBSAs have not been implemented as facility-payer contracts; however, pressures to control health care costs have fostered a new impetus for designing and implementing novel financing mechanisms for health care. Cancer is undergoing a surge of innovation—the majority of FDA approvals in the past 3 years have been for drugs in oncology. Before they are used widely, PRBSAs could be implemented in selected settings in the context of prospective controlled experiments, with careful monitoring of their impact on patient outcomes and system costs as well as patient and provider acceptance. Provider systems or networks with adequate electronic medical records, strong support from billing offices, and a culture of innovation are the most likely candidates for novel financing models such as PRBSAs for genome-directed therapy.

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