Genomic Testing and the Quality of Care: Exploring the Impact of Healthcare Reform

Proceedings from the Thomas Jefferson University Genomics Summit Conference, September 2012

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Genomic Testing and the Quality of Care: Exploring the Impact of Healthcare Reform
Proceedings from a Roundtable Meeting, September 2012

On September 21, 2012, the Jefferson School of Population Health at Thomas Jefferson University in Philadelphia, convened a roundtable meeting of opinion leaders representing key stakeholder groups—oncologic researchers and clinicians, payers, health economists, health technology organizations, policymakers, and community health advocates—to discuss the impact of healthcare reform on genomic testing and the quality of care for patients with cancer.

Moderator David B. Nash, MD, MBA, articulated that the Affordable Care Act (ACA) has set the tone for the overarching theme of the meeting—how to achieve the best possible health outcomes at the best possible price without harm to patients—and described its implications for providers with the succinct statement “No outcome, no income.” The meeting focused on the delivery of value-based care in oncology, with an emphasis on the role played by genomic testing in clinical practice.

The meeting featured 4 plenary presentations designed to address the impact of healthcare reform on the utilization and delivery of oncology resources. In his opening presentation, John Hornberger, MD, MS, discussed whether personalized medicine is cost-effective and explained the challenges in determining the clinical utility of health technology interventions, including genetic testing. Subsequently, William J. Gradishar, MD, FACP, reviewed the barriers and opportunities associated with the adoption of personalized medicine into breast cancer oncology, focusing on organizational constraints and the need for multistakeholder consensus.

Barry V. Forman, PhD, delivered a provocative presentation that addressed the question of value in cancer care and the challenges faced by community oncologists. Finally, Matthew R.G. Taylor, MD, PhD, described the shift from diagnostic to predictive genetic testing, noting that internists are likely to play a vital role as genetic testing becomes increasingly integrated into clinical practice.

Following the plenary presentations, Dr Nash moderated a spirited interactive session that allowed the multidisciplinary panel to provide their unique perspectives on the role of genomic testing in the future healthcare landscape, particularly in the area of oncology.

Is Personalized Medicine Cost-Effective?
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The field of medical economics in the past decade has seen unprecedented evolution and expansion of cost-effectiveness, health economics, evidence-based medicine, and comparative effectiveness research. Those interested in what is increasingly being referred to as “valuation research” ask the fundamental question, “What is the true value of a particular diagnostic test or a medical intervention?” From the answer to this question, policymakers can then make more informed decisions about adoption of the technology, and how much to pay for it.

The value of a medical intervention or diagnostic tool inherently lies in addressing 3 distinct questions:

1. **Does it have predictive ability?** This question pertains to the ability of technology to predict the present (ie, diagnosis) or future (eg, prognosis or chemoresponsive-ness) “state of nature.” These kinds of predictions are made possible through what is called clinical validity studies—that is, studies with sufficiently large, representative sample populations, relevant and accurately measurable end points, and a rigorous methodology for determining whether a personalized medicine technology can reclassify patients into separate classes or groups.

2. **Is it clinically useful?** This question relates to the technology being used appropriately in the population for which it was intended, and the ability of the technology to influence clinical management and, subsequently, outcomes. This is also called clinical utility. Clinical validity involves 2 important concepts: “discrimination” into distinct groups, and the ability to accurately predict...
end points based on class, called “calibration.” Evidence in support of clinical validity does not necessarily mean evidence in support of clinical utility. For example, a 10-year study may conclude that a particular test can accurately discriminate patients into separate risk groups, but it may not yet have been shown to alter practice patterns.

3. Can we afford it? The substantial and unsustainable rise in healthcare costs has made affordability essential to purchasers of healthcare technologies and to society overall. For the purposes of this discussion, the term “purchaser” may refer to payers, hospitals, physicians, patients, and any stakeholder responsible for the monetary consequences of adopting a medical intervention, be it a product, treatment, or technology.

The modern era of research to assess the valuation of new technologies in healthcare began in the 1970s. Since then, a number of notable methodological innovations have evolved, including a framework to evaluate the clinical validity of tumor markers, developed by Hayes and colleagues. By contrast, best and pragmatic practices for demonstrating clinical utility continue to be a more active area of debate. In a May 2012 workshop sponsored by the Institute of Medicine (IOM), participants agreed that evidence on clinical utility is essential for informing population-based policies on new technologies.

A number of papers have been published on best and pragmatic practices for demonstrating clinical validity, and the reader is referred to many of the fine articles by Richard Simon and his colleagues, written over the past 10 years. By contrast, best and pragmatic practices for demonstrating clinical utility continue to be a more active area of debate. In a May 2012 workshop sponsored by the Institute of Medicine (IOM), participants agreed that evidence on clinical utility is essential for informing population-based policies on new technologies.

There was limited consensus, however, on what constitutes sufficient evidence to demonstrate clinical utility.

In response to this “standardization gap,” our firm started working on a standardized framework for grading the quality of evidence on clinical utility of personalized medicine products. The following lists include important factors discussed with our research sponsors, some of which were mentioned in presentations at the IOM meeting:

- **Prospective versus retrospective.** Prospective studies have the advantage of measurement that takes place in real time. Retrospective studies, by contrast, are easier to conduct, but their findings may have limited utility. The data source is a key consideration with retrospective studies.
- **Type of control.** Pre–post comparison of decisions (preimposed “self-controls”) versus matched independent controls.
- **Directly observed versus extrapolated end points.** If end points cannot be directly observed, the researchers may rely on extrapolated end points.
- **Choice of comparator.** Comparators include guidelines, other tests or algorithms, or previous “real-world” published findings.
- **“Real world.”** Real cases versus hypothetical cases.
- **Choice of statistical method.** Methods include estimation (generalized estimating equations, mixed effects); correlation between physicians and cases (eg, more physicians, fewer cases per physician); and sample size computations. The choice of methods and metrics is critical to the accurate reporting of the study findings.
- **Comparative effectiveness.** A majority of cases from tertiary referral centers versus a greater proportion of cases that are representative of the settings in which the test will be used.

To illustrate these principles, our research group recently published a systematic review of clinical validity, clinical utility, and affordability studies for new molecular assays intended to predict recurrence outcomes in patients with early-stage breast cancer. Such a study is relevant for several reasons, including the ability to compare different assays, and to evaluate how the use of tests and decisions varies among studies and across different settings. The study identified 9 retrospective and 6 prospective studies that met the predefined inclusion/exclusion criteria for assessment of clinical validity (there were other studies that focused on clinical validity and affordability). Of the 15 studies identified, 10 pertained to Oncotype DX, 1 to MammaPrint, and 4 to Adjuvant! Online. Studies generally reported changes in decisions when using the assays; the largest change was reported with Oncotype DX (range, 21%-74%). The study identified 9 retrospective and 6 prospective studies that met the predefined inclusion/exclusion criteria for assessment of clinical validity (there were other studies that focused on clinical validity and affordability). Of the 15 studies identified, 10 pertained to Oncotype DX, 1 to MammaPrint, and 4 to Adjuvant! Online. Studies generally reported changes in decisions when using the assays; the largest change was reported with Oncotype DX (range, 21%-74%). The study identified 9 retrospective and 6 prospective studies that met the predefined inclusion/exclusion criteria for assessment of clinical validity (there were other studies that focused on clinical validity and affordability). Of the 15 studies identified, 10 pertained to Oncotype DX, 1 to MammaPrint, and 4 to Adjuvant! Online. Studies generally reported changes in decisions when using the assays; the largest change was reported with Oncotype DX (range, 21%-74%).

The systematic review also evaluated whether the studies were based on comparison with guideline-recommended practices versus what actually happens in practice settings. One of the studies is illustrative of the emerging emphasis on the effects in real-world settings. The Oncotype DX breast cancer assay study was conducted in collaboration with a large US payer, Humana. Using a claims-based registry of 952 women, the investigators examined the likely impact of Oncotype DX on the use of adjuvant chemotherapy and affordability. The study showed that patients predicted to be at low risk for distant recurrence of breast cancer within 10 years were far less likely to receive adjuvant chemotherapy than
those at moderate or high risk. These data were linked to evidence on the effectiveness of adjuvant chemotherapy based on risk; using modern statistical modeling techniques, the assay was projected to substantially increase the life expectancy of a typical patient and improve her quality of life (QOL).

In addition to the effect of a test on decisions and patient well-being, greater interest has been generated in the affordability of personalized medicine technology. Policymakers are increasingly concerned about the rising cost of healthcare, expressing a preference for more direct evidence on the long-term clinical and economic consequences of decisions, particularly in their specific clinical settings. Given the nature of some technologies, such as a test that predicts recurrence risk at 10 years, it is often difficult to accumulate prospective evaluations of sufficient duration that are likely to show a meaningful and timely impact on outcomes. One problem is that with the current pace of personalized medicine technology development, the findings from such studies are often obsolete before data collection has been completed. Alternative study designs include using retrospective registries, which can provide insight into how a test might have influenced decisions and outcomes based on practice patterns from years past. Another approach is to simulate outcomes using statistical modeling techniques from the principles of decision-based theoretical science.

In the systematic review, we identified 11 studies on the economic implications of predictors of outcomes in early-stage breast cancer. Initial studies compared the test with clinical practice guidelines, such as those from the National Comprehensive Cancer Network (NCCN)
and the St. Gallen International Breast Cancer Expert Panel. Later studies compared the test with experience in real-world practice settings. It was found that, relative to guidelines, the use of such tests as Oncotype DX, MammaPrint, and Adjuvant! Online was associated with chemotherapy cost-savings. Later studies, such as the one our group conducted in collaboration with researchers at Humana, in which the comparator was actual practice, demonstrated savings as well.7

The experience with the test outside the United States was found to differ, as was expected. The cost of chemotherapy regimens in other countries is typically lower than that in the United States. Hence, although the test may increase the cost, it also has been found to be cost-effective (Table). This was demonstrated in a study from Israel,8 and similar findings have been presented in studies from Ireland, the United Kingdom, Canada, Singapore, and Japan.

In all such assessments, it is often useful to compare technologies with a 2-dimensional map, in which the change in costs is plotted against the clinical benefit, as shown in the Figure. The benefit is often assessed using the standardized quality-adjusted life-years (QALYs) measure. A QALY accounts for 2 different dimensions of patient well-being: duration of life and quality of a representative patient’s life. In the figure, the lower-right quadrant reflects a gain in QALY with lower costs. This is the ideal situation, which suggests the need for rapid adoption of a technology. The upper-left quadrant is the worst situation, in which a technology is more costly and may be harmful to patients (lower QALYs). The blue area in the upper-right quadrant represents the region of cost-effective technology that increases QALYs but also increases costs. However, this is the region in which the benefits are perceived as outweighing the costs. The white region in the upper-right quadrant is where the benefits are considered insufficient to justify the costs. Finally, the lower-left quadrant is where there is potential harm but also cost-savings. The blue region is unusual, because there is a perception of sufficient cost-savings to accept the harm to patients, which researchers have termed “decrementally cost-effective.” This is a situation much like that of a lifeboat, where extreme rationing may be needed for the greater good of all in the lifeboat; this is atypical for most developed countries not at war or for other crises that affect national wealth (that is, where year-to-year budgeting is generally more predictable). The white region in the lower-right quadrant is where the cost-savings are insufficient to accept the level of harm to patients.

Although affordability studies of drugs have been conducted for more than 2 decades, such studies are less common for personalized medicine technologies, largely as a result of the nascent development and commercialization stage of these technologies. As the field has evolved, professional societies, such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM), have published guidelines regarding best practices in affordability studies of health technology. The ISPOR recommendations, first published in 2003,9 were recently updated in a joint collaboration with the SMDM.10 The guidelines focus on issues related to the validity and credibility of the research methods, discussing in detail topics such as structural validity, parameter validity, mathematical validity, internal validity, external validity, calibration with real-world practice, and interface validity.

We applied these principles systematically in a study of a multigene reverse transcriptase-polymerase chain reaction (RT-PCR) colon cancer assay, using the NCCN colon database as a baseline comparator.11 Specifically, we evaluated the outcome of the decision regarding whether to provide adjuvant chemotherapy for 2 groups of patients—those assessed using current risk-assessment tools and those assessed using the multigene RT-PCR assay in addition to current risk-assessment tools. The study included current methods for assessing recurrence risk, such as tumor stage, histologic grade, lymph node sampling, and lymphovascular invasion.8 According to these findings, if risk assessment is conducted using the multigene assay as an adjunct to these traditional clinicopathologic markers, substantially less adjuvant chemotherapy will be recommended for older patients, especially those who are likely to die of other causes or who have an increased risk for adverse events associated with chemotherapy. As a result, the net effect is a savings in costs.
The standards for conducting research on clinical validity, clinical utility, and affordability have evolved and continue to improve. Some issues remain complex, and consensus on best research practices can, at times, appear elusive. Ongoing concerns that plague reviewers of these studies include the use of inappropriate comparators, reliance on evidence that cannot be generalized to real-world settings, time horizons for studies that render the findings obsolete by the time the study has concluded, and judgments of quality in study design and interpretation that are based on ad hominem criteria (ie, who wrote it?) rather than on a thorough scientific review of the evidence.

It is notable that the manufacturing sector has variable perspectives on the importance of the field of clinical utility and affordability research. Some of the ambivalence stems from the fact that this field is still in its early stages, and experience with a range of technologies is growing. There remains ongoing uncertainty and lack of consensus regarding what policymakers consider to be sufficient evidence. We have found that many payers are reluctant to discuss explicitly measures of patient benefit, such as QOL or the related concept of QALY. A particularly challenging issue is that policymakers may request time horizons of no more than 2 to 5 years with respect to the benefit of the technology rather than projecting to the lifetimes of patients. This is explained as the typical duration in which a patient is enrolled in a commercial insurance plan. Yet, according to survey research, patients have indicated that they prefer decisions to be based on the more reasonable assumption that they will be alive beyond 5 years. This disagreement between the preferences of patients and the policymakers who are making decisions on their behalf is referred to as the “principal-agent problem,” whereby the agent (ie, the insurer) may not be making a decision that is reflective of the interests of the principal (ie, the typical patient enrolled in the plan). Reluctance to discuss costs in an open and transparent manner also has been expressed by US governmental agencies. As evidenced by the debates on the ACA, the US political climate makes it difficult for US agencies to declare explicit thresholds for clinical benefits, cost-savings, or cost-effectiveness, for fear that the manufacturing sector will begin to set prices explicitly to meet the upper limits of these thresholds and, thereby, drive up costs.

For this presentation, I was asked the question “Is personalized medicine cost-effective?” In a career in which I have participated in dozens of analyses and have been a reviewer and/or a journal editor of hundreds of related investigations, I have found the answer to be “yes” most often when the product manufacturer and/or sponsor (a nonprofit, for-profit, or governmental agency) is committed to a culture of best practices in its science and technology evaluation, and has decided that affordability should be a feature of the product profile. In instances in which it seems that affordability was marginalized at the most senior strategic levels, then the answer is more likely to be “no.” As affordability becomes elevated in importance—as many predict—I anticipate and am encouraging senior-level strategic review to include those with clinical and economic expertise who can be seen as credible in designing the necessary studies that will effectively translate the promise of a personalized medicine product into one that is clinically useful and affordable. The path forward remains a commitment to the design and implementation of studies that have clear and pragmatic research objectives, well-defined and agreed-upon comparator endpoints, a sample of patients and physician participants that reflect the characteristics of real-world practice settings, quality data collection, state-of-the-art analyses and interpretations, and in which the evidence translates into credible affordability. When these elements are in place, policymakers can—and should—more easily adopt the technology as a solution to the cost-effective improvement of patients’ lives, on an individual basis and with respect to the health and welfare of the overall population.

Author Disclosure Statement

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References

Barriers to and Opportunities for the Use of Personalized Medicine in Patients with Breast Cancer

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The oncology community’s understanding of breast cancer has evolved considerably over the past 2 decades. Nevertheless, long-term prognosis remains poor for most patients with metastatic disease. However, oncologists are now able to stratify patients into specific subsets and to manage them differently. In some cases, this stratified treatment, which is often referred to as personalized medicine, has yielded improved outcomes. For example, in breast cancer, patients with endocrine-responsive disease are more likely to benefit from endocrine therapy; conversely, non–endocrine-responsive patients are unlikely to benefit from such treatment. Oncologists use these biomarkers to “tailor” or personalize treatment, depending on the presence or absence of the marker.

Similarly, fluorescence in situ hybridization (FISH) testing is often performed to determine whether patients have extra copies of the HER2 gene. Although some questions remain regarding the clinical utility of FISH testing, trastuzumab is often added to chemotherapy in FISH-positive patients. Combination treatment with trastuzumab plus chemotherapy has demonstrated improvement in overall survival among FISH-positive patients; however, no benefit was reported in FISH-negative patients.

The quality of the studies used to evaluate biomarkers is of critical importance. Several years ago, it was thought that the presence of the cytochrome P450 2D6 (CYP2D6) enzyme might help guide oncologist decision-making regarding endocrine therapy in patients with breast cancer. It was postulated that patients respond differently to tamoxifen, based on the way in which they metabolized CYP2D6. Initially, retrospective studies seemed to support this hypothesis, and some oncologists began recommending the addition of tamoxifen accordingly. Subsequently, however, larger, more rigorous trials with thousands of patients have shown that a CYP2D6 activity score does not predict breast cancer recurrence among patients receiving tamoxifen.

Although the medical community is moving toward an era of personalized medicine, it may be more accurate to refer to the current treatment paradigm as stratified medicine, because therapy is being tailored to subpopulations of patients with certain clinical or biological characteristics. For example, breast cancer has been segmented into a variety of subsets, which in some cases have been further subdivided. Clinicians assign prognoses to these different subsets and recommend treatments that are specific to them. With regard to genomic testing, the science has not reached the point at which oncologists are able to individualize treatment for every patient with cancer.

One way for oncologists to personalize therapy is to provide optimal chemotherapy. Some oncologists have a tendency to significantly reduce the amount of medication in overweight and obese patients. Studies have demonstrated, however, that dose reductions in obese patients are associated with poorer outcomes. In fact, dose reductions in obese patients often confer the side effects of chemotherapy, without the clinical benefit. As the obesity epidemic continues, concerns exist that many obese patients with cancer are being undertreated.

The NCCN publishes and maintains clinical guidelines that include treatment recommendations for a broad range of malignancies. The NCCN follows an algorithm-based approach that integrates clinical and biological factors; recommendations are graded in accordance with the strength of the evidence. Although the NCCN makes its recommendations based on the best available evidence, a number of intervening variables may affect patient care, including comorbidities, adherence behaviors, insurance, and quality of care. The guidelines cannot account for all possible barriers to optimal therapy and patient outcomes. In many cases, the clinician must exercise his or her professional judgment in making treatment decisions when nonclinical variables come into play. In addition, considerable interpatient variability exists with respect to patients’ perceptions of the benefits and risks associated with a particular course of treatment. As a result, clinicians typically make shared decisions in consultation with the patient.

The NCCN decision-making involves a number of factors. Levels of evidence are assigned to the treatment algorithms, based on the consistency, extent, and quality of the evidence. Although the data are objective,
application of the data has a subjective component, and the specified cutoffs for treatment or no treatment, testing or no testing, and the weighing of risks versus benefits reflect the values and preferences of the experts who write the recommendations.

Most of the algorithms currently contained in the NCCN guidelines are supported by Category 2 level of evidence. In rare occasions, the evidence is supported by a high-level, randomized phase 3 trial, and involves a uniform, absolute consensus regarding the recommendation. In other cases, however, the evidence is relatively weak and is cited as Category 3, if it is included in an algorithm at all.

The NCCN seeks to avoid influence by outside parties and requires that its members report any conflicts, which are cited as disclosures at the beginning of every meeting. These disclosures are published and are available online. Evidence review is an ongoing process, and recommendations frequently modify new evidence that enters the literature. Therefore, there may be ad hoc discussions that result in a change in the guidelines or a consideration of a change.

The 4Rs in an oncology collaborative program (Right information, Right care for the Right patient at the Right time) was developed by individuals interested in efficiencies, focusing on the medical home and new developments in clinical cancer care. The initial model was based on breast cancer and subsequently expanded to other disease sites. This approach involved convening a number of multidisciplinary roundtable meetings that included clinical experts, payers, patients, and representatives from oncology societies, to evaluate the current models for cancer care. The program endeavored to describe the impact of care delivery, reimbursement, and organizational barriers, and characterized the consequences for overall quality of cancer care.

A total of 51 in-depth interviews were conducted with clinicians, patient advocates, and payers. The interviews revealed the existence of 2 interrelated types of barriers to personalized medicine:

- Poor timing and sequencing of genetic tests relative to care decisions
- Provider reimbursement and patient benefits.

All 3 stakeholder groups (ie, clinicians, payers, and patient advocates) identified provider reimbursement and/or patient benefits as a frequent barrier to treatment. Specifically, a genetic test may reduce drug or procedure reimbursement (ie, if not prescribed or performed, the clinician loses revenue); the time spent reviewing test decisions with patients is poorly reimbursed; supportive and genetic services are not reimbursed; and patient out-of-pocket costs for tests may be prohibitive, thereby creating a disincentive for patients and for clinicians to order the test.

Clinicians and patients (and, to a substantially lesser degree, payers) identified poor timing and sequencing of tests relative to decisions as a barrier. For example, it can be difficult to coordinate tests relative to treatment decisions because of the complexity and length of the testing process, because ordering is frequently conducted outside of the physician’s office, and because ordering physicians often lack the tools necessary to coordinate the various participants. In addition, the prior authorization process delays treatment and often involves staff outside the physician’s office, over whom the physician has little control. The complexity of some genetic tests and the ensuing consultative decision-making process may also serve as a barrier in some cases. Furthermore, physician perceptions with regard to the pace of treatment may not necessarily align with patient priorities and preferences.

As a result of these barriers, tests may be ordered but not used in the treatment decision, the treatment decision and/or treatment may be delayed, or the test may be postponed or avoided. Regardless of the specific cause, the patient may receive less-than-optimal care in each of these scenarios.

Overall, the interviews revealed substantial discordance between clinicians and payers, patient advocates and payers, and, to some degree, patient advocates and clinicians, as illustrated in the Table.

Ongoing debate persists in the area of oncology diagnostics regarding testing protocols and technologies, which is closely related to issues of quality and variability in cancer biomarker testing. Previous interviews with breast pathologists, oncologists, and payers have revealed that organizational barriers, not just technological issues, may impact testing quality and variability. There is a lack of transparency of diagnostic quality among laboratories and physicians, patients, and payers; a lack of organizational decision processes for diagnostics within cancer centers; and misaligned incentives for laboratories within medical centers. In addition, some National Cancer Institute-designated cancer centers are unaware of the collective biomarker practices used by their organization.

It is vitally important to formally recognize these and other barriers to personalized medicine, although we may have tacit knowledge of them. Effective solutions will require not only a productive dialogue, but also a mutual awareness of barriers. As patient-centered solutions continue to evolve, it is reasonable to expect a greater degree of engagement from patients and from patient advocates. Furthermore, current healthcare initiatives should explicitly include considerations for personalized medicine, and efforts to increase care coordination should clearly document a standardized process for ordering genetic tests.
Similarly, new oncology payment models should address reimbursement barriers and provide incentives for the appropriate use of diagnostic testing in the clinical decision-making process. Although national solutions could take years to address effectively, individual clinicians, medical centers, and payers all can take steps now to proactively recognize and address the barriers to personalized medicine. For example, the Robert H. Lurie Comprehensive Cancer Center of Northwestern Medical Center in Chicago, IL, is establishing a new model (screening tool and protocol) for timely genetic counseling and testing of newly diagnosed patients. Ultimately, the goal is to have a more streamlined system that minimizes delays and leads to truly personalized care for each patient.

Author Disclosure Statement
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References
Deriving Value in Community Oncology
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Macroeconomic pressures are affecting multiple domains of the US socioeconomic system. By 2022, mandatory government spending for Medicare, Medicaid, and Social Security programs will account for more than 50% of the nation’s total annual budget. In this context, the 20-year pattern of escalating costs of cancer care, combined with the aging population base, has attracted much attention as a potential driver of continued unsustainable expenditures. Although the cost of healthcare in general has increased at a rate of approximately 9% annually, cancer-related medical and drug costs have increased at rates of 12% to 18% and 20%, respectively.1

The federal government has enacted several initiatives to curb overall healthcare spending, beginning with the introduction of the sustainable growth rate methodology in 1997. The shift away from Medicare Part B drug reimbursement based on average wholesale price to average selling price (ASP) enacted by the Medicare Modernization Act of 2003 was an innovation disproportionately affecting community oncology, the primary cancer care delivery mechanism. Ongoing downward adjustments in the Medicare Physician Fee Schedule and the potential cuts stemming from the 2011 Budget Control Act provision to sequester 2% of the national budget added further negative pressure. Private payers, emboldened by the reduction in drug payments by Medicare, have followed suit in lowering drug reimbursement, implementing preauthorization procedures, and experimenting with alternate payment models to manage the utilization of cancer drugs and services. Finally, legislative mandates to develop payment methodologies through the provisions of the ACA are creating uncertainty that many believe threatens the viability of private practice–based community oncology care.

Societal Call for Value
As the overarching economic pressure to contain healthcare spending rises, various constituencies are calling for a fundamental shift in how we remunerate healthcare. The core proposition is to reward “value” in healthcare, as opposed to “production.” Of note, the concept of value intertwines the quality of care delivered in ratio with the cost of care. Although many particulars are yet to be codified and most efforts to date devolve and become a straightforward pursuit of cost reduction, it can be argued that the new language of medicine is an ineluctable diction, in which value must be demonstrated and additional levels of value pursued to avert the ongoing threat of less sophisticated reductions in healthcare reimbursement. The inexorable march toward value is now spearheaded by the resilient ACA, which includes an ingenious, assertive subset of programs that press the nation toward a grand experiment with value-based care.

It may be argued that community oncology and the buy-and-bill model of drug purchasing have been particularly vulnerable to being the target of legislation and reimbursement management measures, because the profession as a whole has not adequately delineated its value proposition or differentiated itself from alternative delivery modalities—namely, cancer hospitals, academic medical centers, and regional hospital outpatient clinics. In addition, it may be cogently disputed that the deleterious implications of various alterations in reimbursement of the primary delivery mechanism for cancer care have not been effectively enunciated to the larger healthcare community. Finally, it may be posed that community oncology stakeholders have been reticent to embrace progressive approaches to value-based cancer care, which has positioned community oncology to be subject to the decisions of others rather than self-determining the manifestation of the value paradigm in cancer care.

As the cost of a year of cancer treatment has reached unsustainable magnitudes, it is imperative for community oncologists to lead the discussion about the value that can be achieved despite the reality of the continually rising high costs of hospitalizations, emergency department visits, diagnostic testing, and cancer drugs. If left to other professional segments, including those within the oncology community, critical definitions will be less sensitive to the idiosyncratic characteristics of community-based cancer care.

As illustrated in Figure 1, defining value as a mere ratio between quality and costs is too simple for the real world of community oncology. On the one hand, an examination of the relationship among cost, quality, and value shows that the value quotient of high-cost therapies (ie, ≥$100,000 annually) may provide acceptable quality but only moderate relative value. In the new language of oncology, therapies once accepted as clearing minimal scientific bars are less defensible if they provide limited incremental value at an equal or greater cost than a previous treatment.

On the other hand, community oncology has failed to lead in the debate on poor or inadequate care and, as a result, has experienced professional criticism that...
otherwise might have been levied at other targets in the cancer care continuum. Without clear delineation of a quality floor, community oncology will be vulnerable to cost-cutting pressures encouraged by reimbursement models that integrate, bundle, or capitate expenditures. It is in the best interests of community oncology to establish the upper and lower thresholds of value and risk, and define these parameters in ways that may prevent deterioration in the delivery of high quality of care.

This article explores ways to achieve higher levels of value in cancer care. Before turning to positive assertions, it is important to note what has not worked for the healthcare community at large and for oncology in particular (Table 1).

One of the primary objectives of science is the elimination of possibilities. A scientific approach to the evolution of healthcare management would ask what programs have been shown not to work or for which programs is there little evidence available to assume they work. These negative options should be approached with caution, if not avoided altogether, in favor of new approaches or those that are suggested to likely be demonstrable, generalizable, and replicable.

What Has Not Worked

Aside from lowering reimbursement rates, the most ubiquitous utilization management strategy implemented by payers for specialty drugs is prior authorization (PA). Yet, denials of oncology products are rare, likely because oncology medications are infrequently used off-label.2 Only 1 in 5 payers report successfully limiting inappropriate utilization with PAs in oncology, and only 27% of payers believe that PAs are fully achieving their intended management objectives.3 Although it seems inevitable that PA will play a prominent role in the future of cancer care, it is reasonable to question whether the money and human capital expended on PA would be better directed elsewhere given the expense of PA for payers and providers.4

In addition, pay-for-performance (PFP) and shared-savings programs have failed to generate a pattern of consistently positive results. Medicare has sponsored demonstration projects for the past 2 decades in an effort to enhance quality and improve the efficiency of healthcare delivery of the fee-for-service program. There have been 2 major categories of projects—disease management/care coordination demonstrations and value-based payment demonstrations. Neither has consistently shown cost-savings, except for a single cardiology-based bundled payment demonstration for patients requiring coronary artery bypass graft surgery that yielded modest savings,5 which has been qualified, if not questioned, in a subsequent analysis.6

A number of explanations for the anemic showing of quality improvement programs have been posited. One explanation suggests that hospital systems shift costs, so that when a program reduces costs in one category, the dynamic system stimulates other aspects of care that increase costs elsewhere, thus offsetting savings.7 In addition, because only a fraction of patient care costs are truly variable, the potential effect size of some programs may be limited from the outset.7 PFP incentives have been of great interest to payers and to providers, but a recent analysis of the poor overall results concludes that incentives have frequently been insufficient or muted by program design, resulting in an estimated $20 billion in wasted resources each year.8

Alternatives to buy and bill have also been unsuccessful in establishing positive value trends. The buy-and-bill model is the process via which independent physician offices buy and maintain inventory of oncology drugs and subsequently bill for medications as they are administered. Under this model, physicians bear financial responsibility for the initial expense associated with oncology agents, and the onus falls on the physician to collect from both the payer and the patient in order to recover the cost of the initial outlay for the drugs.

Although, buy and bill remains the dominant mechanism for delivering drugs in oncology,9 including to rural areas,10 there has been a shift away from this approach...
toward specialty pharmacy providers, because of an increase in the minority proportion of oral oncology products, as well as through the influence of payer-owned specialty pharmacies and pharmacy benefit management companies seeking broader control of the pharmacy and the medical benefit. Whereas oral oncology agents offer a number of patient advantages, adherence rates for oral and injectable oncology medications received primarily through the pharmacy benefit are relatively poor and are in line with other prescription products. In contrast, nonadherence to oncology agents received through the medical benefit in physician offices is largely accepted as minimal. The high rate of nonadherence and poor persistency is a challenge to value projections if it assumed that shifting products from the medical to the pharmacy benefit would result in a corresponding decrease in adherence and persistency.

Specific alternatives to buy and bill, such as “brown-bagging” or “white-bagging” of oncology agents, have also been unsuccessful in demonstrating the potential to produce higher levels of value above the existing buy-and-bill model. The grandest attempt at an alternative to buy and bill was the Competitive Acquisition Program, which failed because of lack of vendor and provider participation. Furthermore, the acquisition price of drugs through brown-bagging or white-bagging has been reported to be 17% higher than those purchased by the physician’s office. Approximately 20% of the drugs shipped to the patient or to the physician’s office through brown-bagging or white-bagging fail to be used, because of clinically necessary changes in dose, drug selection, or overall treatment strategy.

Once delivered to the patient or to the physician’s office, these expensive medications cannot be returned, resulting in enormous waste. Approaching value with a 17% higher acquisition price and an upfront 20% wastage of oncology drugs is a serious impediment to value models that propose alternatives to the buy-and-bill model.

**What Has Worked**

Despite the challenges, several aspects of cancer care have produced relative value in the marketplace, and the backdrop of failed efforts provides stark relief for those with supporting evidence.

Incremental innovation has helped to create value in cancer care. Primary research discoveries in the 1970s generated an explosion of clinical trials in the 1980s and 1990s, resulting in an evolutionary burst in US Food and Drug Administration (FDA)-approved oncology drugs and indications beginning in the 1990s. Virtually the entire modern oncology drug portfolio was approved in the past 20 years; we now have an FDA-indicated drug specific to most major tumor types and lines of therapy within major tumor types. The emergence of the portfolio of modern supportive care drugs allowed care to move from the inpatient site of care to outpatient delivery avenues, making the widespread access to cancer care in the community possible.

During the past 20 years, the cost of cancer care has increased in absolute and in relative terms. The avail-

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>What Has Worked and Not Worked to Generate Value in Oncology</th>
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<tr>
<td><strong>What has not worked</strong></td>
<td><strong>What has worked</strong></td>
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<td>Prior authorization</td>
<td>Incremental innovation</td>
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<tr>
<td>Increased practice and payer operational costs</td>
<td>Transformation of the cancer drug portfolio</td>
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<tr>
<td>Failure to change care</td>
<td>Improved survival rates</td>
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<tr>
<td>Failure to achieve savings</td>
<td>Creating a competitive field of drugs, becoming generic or biosimilar alternatives</td>
</tr>
<tr>
<td>Pay for performance and quality payments</td>
<td>Supply chain</td>
</tr>
<tr>
<td>Inconsistent and frequently negative findings</td>
<td>Accurate, timely delivery of complex drugs to every region of the country</td>
</tr>
<tr>
<td>Alternatives to buy and bill</td>
<td>Near at cost; low net profit margin</td>
</tr>
<tr>
<td>Higher drug acquisition price</td>
<td>ASP plus buy and bill</td>
</tr>
<tr>
<td>More drug wastage</td>
<td>Lower cost of oncology generics</td>
</tr>
<tr>
<td>Lower patient adherence</td>
<td>Incentivizes use of oncology generics</td>
</tr>
<tr>
<td></td>
<td>Curbs yearly price increases</td>
</tr>
<tr>
<td></td>
<td>Creates risk for physician corresponding to cost of drug</td>
</tr>
<tr>
<td>Alternatives to buy and bill</td>
<td>Community oncology</td>
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<tr>
<td></td>
<td>Maximal access to complex, outpatient treatments</td>
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<tr>
<td></td>
<td>Less expensive than alternative sites of care</td>
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<tr>
<td></td>
<td>Equal quality to more expensive alternative sites of care</td>
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ASP indicates average selling price.
ability of new agents and increases in access to care, however, are key contributors to positive survival rates among patients with cancer during this time frame. In addition, the cost of cancer care may have been relatively outpaced by improvements in survival, suggesting that the value of cancer care has increased. A recent study by Philipson and colleagues suggests that about $600 billion of incremental value was added by the US healthcare system between 1983 and 1999 above what was generated by the delivery system of Europe when relative costs and improvements in survival rates were considered. Moreover, between 1995 and 1999, an approximate $20,000 increase in spending per patient with cancer was associated with an additional 2.3 years in life expectancy after diagnosis on average. The increase in cancer spending over the past 20 years has been significant, but with the improvements in the ability to deliver care in the outpatient setting, the availability of care in the community, and increased patient survival, the overall pattern of data suggests that incremental innovation has been associated with a positive value trend.

Perhaps more important, incremental innovation is on the verge of generating even greater levels of value in cancer care through the maturing oncology drug portfolio. The oncology portfolio emerging in the 1990s is coming of age, creating the potential for unseen levels of value through previously absent competition and by conversion of existing blockbuster agents to generic and biosimilar alternatives. By 2020, a robust portfolio of generic and biosimilar treatments will inevitably be available in the oncology arena.

Generics and biosimilars are essential components to achieving more acceptable levels of value in cancer care. Under the ASP model, prices typically have fallen dramatically when an oncology agent becomes available in generic form, as illustrated by the precipitous decline in ASP for a number of oncolytic agents, including irinotecan, gemcitabine, and, more recently, docetaxel, and oxaliplatin. This pattern is associated with absolute savings. Assuming equally high manufacturing standards for these generic and biosimilar products, the value of the same unit of care will increase. The precise level of savings with biosimilars is unclear, but the competition created by any level of price pressure will ultimately benefit the consumer. The US Congressional Budget Office estimates that generics and biosimilars will lead to $753 million in savings between 2013 and 2022.

Incremental innovation stemming from pharmacogenomic testing represents a fundamental opportunity to increase value in oncology care. It has been estimated that the ineffective use of diagnostic, therapeutic, and procedural interventions is associated with $250 billion to $300 billion in unnecessary care and $25 billion to $30 billion in disease complications annually. Several studies have demonstrated that pharmacogenomics has the potential to reduce the cost of unnecessary treatment. Pharmacogenomics has the potential to direct the use of these agents and limit the populations in whom they may be effectively applied. This focus, combined with enhanced efficacy, will correspondingly set limits on the overall financial impact of agents that will likely continue to have high absolute cost when viewed in isolation. Pharmacogenomics also has the potential to refine the efficacy of branded products at the end of their life cycle, thereby contributing greatly to value trajectories by enhancing the efficacy of agents whose price is undergoing life cycle decline.

The process of innovation that is responsible for producing generics, biosimilars, and pharmacogenomics is changing the way in which new oncology products are brought to market. Over the next 10 years, bringing a new drug to market will be more difficult than before because new oncology agents will face an increasingly crowded environment, including the lower-cost alternatives of generics and biosimilars. Because oncology agents will be increasingly restricted to niched populations, they will have to demonstrate significant levels of incremental value to merit uptake by an even more cost-conscious marketplace.

The supply chain has also been shown to deliver value. Through competition and innovation in third-party logistics, major wholesalers are able to operate near cost. Although not without room for improvement, this at-cost system is maintaining successful delivery rates across billions of dollars of drugs in every nook and cranny of the country. It is difficult to conceive of a more cost-effective approach to delivering oncology agents across the country. It is estimated that the pharmaceutical industry saves about $45 billion annually by using the existing supply chain—$6 billion of which is related to specialty agents such as cancer medications. Under the conditions of fiscal scrutiny, all elements of the healthcare system deserve attention; however, it is highly unlikely that an alternate infrastructure could be readily developed that will operate successfully at the margins of accuracy and cost currently being demonstrated. Additional methodologies for dealing with gray-market products will further improve the value contribution of the supply chain if these additional solutions are designed in a cost-effective manner.

In addition to incremental innovation and the supply chain, evidence suggests that the buy-and-bill model is effective in creating value under current Medicare payment conditions. A recent study by the US Government Accountability Office of the highest-expenditure drugs paid for under Medicare Part B revealed that the majority of the most expensive agents...
increase in price year over year. However, an examination of the magnitude of the price increases reported suggests the annual price increase for the vast majority of drugs was <6%. This stands in contrast to specialty products obtained, for the most part, through the pharmacy benefit, where most oncology drugs obtained under Medicare Part D have seen substantially higher annual prices based on our analyses.

The reason drugs purchased under Medicare Part B do not experience yearly price increases to the extent seen under Medicare Part D is that manufacturers are limited in the extent to which they can raise prices under the ASP system with buy and bill. Under ASP, Medicare pays a fixed percentage based on the previously reported period. If manufacturers raise the price of an office-purchased drug, the physician must absorb the cost of the price increase until the reimbursement rate catches up. If the price of an agent is increased too much, it makes the drug acquisition price higher than the reimbursement rate for whatever time is left in the ASP payment period. Medications that cost more than Medicare reimburses are referred to as “underwater” drugs. As a result, manufacturers are reluctant to impose large yearly price increases. This dynamic has generated relatively flat annual price increases for agents reimbursed under the buy-and-bill model, in contrast to high annual price increases for oncology drugs delivered through alternative avenues.

Furthermore, contrary to what has been suggested, the buy-and-bill model under current Medicare reimbursement rates encourages the use of generics among community oncologists, because of the risk associated with the fundamental direct and indirect costs of buy and bill (Figure 2).

The notion that ASP and buy and bill encourage physicians to prescribe higher-priced drugs and fewer generics is not supported by utilization trends observed for oncology products having advanced to generic form in the ASP era. The recent series of events with oxaliplatin provides a natural ABAB quasi-experimental analysis, because the drug was initially available in branded form, faced generic competition, achieved branded use again, and is now available as a generic for a second time. The demand for this drug has remained high until today.

These factors elucidate a tremendous value proposition for community oncologists under buy and bill. Community oncology is uniquely structured, with risk related to drug purchasing being the predominant mode of delivering care. Community oncologists operating under buy and bill assume a considerable amount of risk stemming directly from the drug inventory they must purchase, the overhead associated with obtaining and maintaining the drug inventory, the cost associated with the lag between purchasing drug inventory and being reimbursed, the risk of not being reimbursed, and, in particular, by the patient.

In other words, not only is community-based oncology the predominant site of care, but it is also the most cost-effective. Recent data have demonstrated that it is less expensive to provide oncology care in the community than in hospital outpatient settings. As shown in

**Figure 2 Inherent Costs of the Buy-and-Bill-Payment Model**

There are direct and indirect costs inherent to the “buy-and-bill” model

<table>
<thead>
<tr>
<th>14 days</th>
<th>5 days</th>
<th>30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line of credit</td>
<td>Malpractice insurance</td>
<td>Collection management</td>
</tr>
<tr>
<td>Procurement and inventory management</td>
<td>Drug wastage</td>
<td>Bad debt on denials</td>
</tr>
<tr>
<td>Federal and state pharmacy certification</td>
<td>• OSHA, EPA, and state documentation</td>
<td>Delayed payments</td>
</tr>
<tr>
<td></td>
<td>• Hazardous waste disposal vendor</td>
<td>Underpayments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bad debt patient liabilities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Deductible, copay, coinsurance</td>
</tr>
<tr>
<td>Inventory</td>
<td>Administration</td>
<td>Reimbursement</td>
</tr>
</tbody>
</table>

Used with permission from ION Solutions.

| Table 2 Chemotherapy Costs, by Length of Episodes |
| --- | --- | --- | --- |
| Length of episode, mos | Office-managed episodes | HOPD-managed episodes | Percent difference in average episode costs, % |
| Episodes, N | Average episode cost, $ | Episodes, N | Average episode cost, $ |
| 1 | 4601 | 7350 | 1784 | 9903 | 34.7 |
| 3 | 2502 | 19,238 | 1091 | 24,592 | 27.8 |
| 5 | 1601 | 26,979 | 481 | 40,677 | 50.8 |
| 7 | 1091 | 26,395 | 268 | 40,879 | 54.9 |
| 9 | 734 | 26,794 | 127 | 57,384 | 114.2 |
| 11 | 302 | 47,468 | 69 | 63,366 | 33.5 |

HOPD indicates hospital outpatient department.
responsibility will naturally provide a conservative market incremental value to the oncology sector, and delivery biosimilars, and pharmacogenomics will add enormous value, which will be in line with the growth of the treated population. General healthcare market, they presage a new age of viability of oral drugs, IMS Health projects that overall increases on existing agents, and the increased financial and legal risk directly associated with the cost and outcomes of a patient’s chemotherapeutic regimen and supportive care, because of the nature of the independent buy-and-bill model. Therefore, oncologists are financially and legally motivated to manage drug spending; utilize accepted treatments in established areas; and use their own outpatient services, rather than hospital-based services, such as emergency department visits and hospitalization. Evidence suggests that community oncology practices frequently use guidelines and pathways and are likely to participate in clinical pathways or pay-for-quality programs when available23-28, are generally compliant with current evidence-based guidelines in oncology; and use relatively few off-label drugs.3 Because community oncology practices provide shorter wait times and drive times for patients,10 the picture of accessibility, quality, relatively lower cost, and convenience creates a compelling image of the value of the community oncology delivery system.

Conclusion

The combination of incremental innovation, cost-effective supply chain, ASP-based buy and bill, and community oncology has brought us to the precipice of enormous levels of value, as the maturing oncology drug portfolio makes available successive waves of generics, biosimilars, and genomically informed products. Although spending on oral oncology agents will continue to increase at a high rate because of the large number of new oral medications in the pipeline, yearly price increases on existing agents, and the increased financial viability of oral drugs, IMS Health projects that overall spending on oncology agents will be relatively flat and in the range of approximately 3.8% through 2016.29 Although these growth projections may still exceed the general healthcare market, they presage a new age of value in oncology, in which the total cost of cancer care will be in line with the growth of the treated population.

Value is at our fingertips. In the coming years, generics, biosimilars, and pharmacogenomics will add enormous incremental value to the oncology sector, and delivery models that maintain high access and encourage financial responsibility will naturally provide a conservative market as the foundation for an evolving era of cancer care.

Author Disclosure Statement

Dr Fortner is an employee of ION Solutions.
As the era of personalized medicine draws nearer, a need exists to bring genomics to the broader medical community, including primary care physicians. Internal medicine represents one of the largest groups of practicing physicians in the country; nearly everyone will see an internist at some point in his or her life. Currently, the majority of physicians lack an in-depth understanding of the application of genomics to medicine. As the end users of genomic tests, it is imperative that practicing physicians know how to use or interpret genomic tests, and education will be required to face this currently unmet need.

Now that human genome information can be accessed in the laboratory for a few thousand dollars, the playing field has changed substantially. There is reason to believe that we may be reaching an inflection point between qualitative and quantitative medicine, and diagnosis versus prediction (Figure). Many physicians are accustomed to diagnostic, binary thinking. This thought process results in the reactive practice of medicine. Clinical practice is beginning to move from mainly qualitative tests and measures, however, to a more quantitative approach, which offers the ability to be more predictive. Because of the advances in genomics, clinicians are being forced to think a bit differently about the future practice of medicine.

Although educational challenges exist, genetic testing has certainly arrived in clinical medicine. In recent years, many more genetic diagnostic tests have become available to clinicians. Some of these are relatively straightforward germline tests designed to determine whether an individual has inherited a particular disease from his or her parents, and range in price from a few hundred dollars to more than $10,000 for larger testing panels. Increasingly, diagnostic tests are being marketed outside of the genetics community. As a result, there are more genetic tests and, presumably, more physicians, sufficiently trained or not, who are now accessing and using these tests.

The cost per genome has dropped precipitously. In October 2001, the cost was an estimated $100 million per genome. With the introduction of new sequencing techniques, however, a substantial price decrease has occurred. As of July 2011, the cost per genome was approximately $21,000.\textsuperscript{1} The technology has now evolved to the point where genetic information can be obtained for a very low cost.

A seminal example of the potential of diagnostic genetic testing was published in 1999.\textsuperscript{2} A 19-year-old woman was exercising, then went swimming. She was found unconscious in the shallow end of the swimming pool, cardiopulmonary resuscitation was initiated and she was physiologically rescued, but her brain never recovered. The patient died 12 days later. The physicians who cared for this patient suspected that perhaps a genetic defect was responsible for her death. An electrocardiogram (ECG) was performed and an abnormality was detected. The woman had long-QT syndrome, which may be acquired or inherited. The physicians conducted a genetic assay and concluded that the woman had an underlying genetic defect that predisposed her to long-QT syndrome.\textsuperscript{2}

Before 1999, this genetic defect was not clinically diagnosable. There was nothing in the patient’s family history to indicate a definite diagnosis of long-QT syndrome. Because of the assay, the physicians identified a genetic predisposition that contributed to the woman’s death and were able to reach a confirmed diagnosis.

In terms of risk assessment, investigation of hereditary factors has been traditionally conducted via the

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**Figure** The Shift from Descriptive to Predictive Diagnostics

- **Predictive**
- **Inflection point**
- **Descriptive diagnostics**
- **Diagnostic**
- **Qualitative**
- **Quantitative**

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use of family histories, which continue to have clinical relevance today. Consider a different case example. The 18-year-old sister of the deceased patient described above underwent an ECG, which indicated a borderline normal/abnormal QT interval. The ECG was shown to 8 electrophysiology cardiologists, with 4 concluding that it was normal, 3 believing it was equivocal, and 1 declaring it was abnormal. At the time, 2 of the electrophysiologists recommended some treatment on the basis of this healthy woman’s ECG.

ECG testing of other family members revealed that the QT intervals were not entirely normal in the mother and the maternal grandfather. Therefore, it appeared that a genetic defect may have been responsible for the borderline QT intervals. The preponderance of genetic data indicated that an abnormal QT interval was probably responsible for the 19-year-old woman’s death, and there was evidence of QT abnormalities in other family members as well. In the 18-year-old patient, nothing changed with respect to her ECG, her symptoms, or her family history. When the same 8 electrophysiologists were provided with the family genetic data, however, they all concluded that the sister’s ECG was abnormal and recommended beta-blocker therapy. In addition, 3 of them recommended the use of a defibrillator device. In this case, genetic testing directly influenced clinician behavior in the management of the patient.

Family history assessment has long been used to stratify patients at varying levels of risk for hereditary cancer syndromes. More recently, genetic testing has been integrated into risk assessment to establish which individuals in a family might be at risk for the development of a particular type of cancer. As more personal genetic tests become available and prices continue to decline, more and more individuals will have access to these types of information.

Different specialties may have unique perspectives regarding the value of genetic testing. For example, because pediatricians treat children, they are highly motivated to determine the root cause of a medical condition even if they are unable to treat it. Thus, they are more likely to embrace a genetic test that will provide answers for the parents. Conversely, internists treat older populations and tend to be a more pragmatic group. They may hesitate to recommend a genetic test unless the result will be actionable. In other words, internists are less willing to order a test merely for the sake of obtaining certain information. They are more oriented toward managing the condition rather than finding the root cause.

Patients and often physicians are sometimes lured into what has been described as the “magic bullet” approach to medicine. Physicians assume that a patient will take a particular drug as it was prescribed. However, that is often not the reality. In general, all patients are given the same drug (or same category of drugs) for a particular diagnosis. On average, however, use of that particular agent is effective in only 25% to 60% of patients. After 6 months, many people will have discontinued use of the agent for a variety of reasons, including lack of clinical benefit and adverse reactions. For most conditions, however, physicians continue to prescribe the same drug or group of drugs to all patients because they do not have sufficient information to individualize therapy. In the future, the field of pharmacogenetics/pharmacogenomics will have the potential to alter this treatment paradigm.

Before medicine becomes personalized, it must first become stratified. When a physician prescribes a medication, there are different dynamics at work, with many decision points and possible variables that influence the effectiveness of the particular agent. For example, the medication must be prescribed, taken, absorbed, activated if necessary, reach its end target, and have a biologic effect. Geneticists are working to identify genes that may predict response at a number of different decision points, and researchers are attempting to answer the question “At which decision points are genetic markers going to be useful to help manage patients and at which points are they not?”

Regardless of future possibilities, pharmacogenetic testing has some current practical applicability in clinical medicine. A prototypical example involves acute lymphoblastic leukemia—a rare childhood cancer with a historically high mortality rate. The chemotherapeutic regimens used to treat this disease are toxic, and oncologists must balance the therapeutic effect with the myelosuppressive effects of the particular agent. Researchers have found that a small subset of patients have difficulty metabolizing the chemotherapeutic agent used to treat this type of cancer. Using a one-size-fits-all approach, the treatment regimen, not the disease, would be predicted to cause a fatal outcome (because of the toxicity of the drug) in 1 of every 200 patients. Tests are currently available to identify patients who do not metabolize a chemotherapeutic agent, thus allowing physicians to adjust the dose for these patients prior to treatment initiation. Nonmetabolizers respond favorably to a reduced dose, with the authors suggesting that those patients who receive reduced doses will experience better survival outcomes than do normal metabolizers who receive standard doses.

With regard to personalized medicine, genetic testing will allow for more granular stratification of patient subsets in the future. This will permit clinicians to treat different subpopulations more effectively than with the one-size-fits-all paradigm.

Genetic practice has been integrated into clinical practice in the treatment of Fabry’s disease, a rare genetic disorder. In analyzing one specific case of the cardiac variant of the disease, researchers were able to identify the
gene associated with the specific mutation, noting that the genetic defect caused patients to produce a protein in such a way that it could not be metabolized inside the cell by lysosomes. The investigators determined that adding molecular chaperones stabilized the protein, allowing it to fold, be transported, and ultimately metabolized. After treatment, the patient was removed from the cardiac transplant list and went from a New York Heart Association (NYHA) functional status of class IV to NYHA class I. This breakthrough was accomplished with the use of an agent that was designed specifically for a particular mutation. More recent clinical trials have been initiated to investigate similar individualized therapies with molecular chaperones in patients with other rare diseases.

Advances in genomics have resulted in more predictive models and quantitative assessment tools becoming available to the medical community. The goal is to make these tools more practical, so that rather than being an academic exercise, they have the ability to add value to risk assessment, particularly for primary care practitioners. Overall, the aim is to create new ways of classifying disease so that we can diagnose and treat patients more effectively at an affordable cost, thus leading to improved outcomes. This is a very different approach from the way in which medicine traditionally has been practiced.

Author Disclosure Statement

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References


The Application of Genetic Testing into Clinical Practice

As genetic tests continue to be commercialized and become more widely available for use in clinical practice, the value proposition of genetic testing needs to be better elucidated and communicated to key stakeholders. Physicians require education to help them interpret and present test results to their patients. Patients need to be educated regarding the potential clinical benefits and limitations of genetic tests. Commercial and government payers must recognize both the clinical and the economic impact of genetic tests in terms of improved outcomes and cost-savings. In this regard, development of a consensus framework with standard metrics to evaluate clinical validity and utility would greatly assist payers in the assessment of genetic tests.

A number of tests are available for the detection of genetic abnormalities, most of which are currently used for diagnostic purposes. As the science continues to evolve, however, it is expected that more predictive tests will become available in the future. The prospect of predictive testing is particularly exciting to clinicians because, in many cases, the results may lead to an actionable response. The fact that a genetic test triggers a decision, however, also underscores the need for improved communication and shared decision-making between clinicians and patients. To make a truly informed decision, clinicians will often need to tailor their recommendations to each patient. The following exchange highlights this issue.

Dr Lundquist: We need to think about how to frame information for the patient to facilitate informed decision-making. A patient with a different frame of reference may select an option different from what the clinician is recommending. That’s not wrong or right. We as physicians may think that 99% of the time we would choose...
a particular option, but a patient may have a different perspective and say, “I’m not willing to take that risk.” Whether it is financial or socioeconomic, there may be many intervening patient variables affecting the decision.

From a systems perspective, we need to think about building in decision criteria to guide physician behavior as well. For example, can we build in criteria to ensure that the physician does not underdose the obese patient?

Dr Hornberger: As physicians, we need to be able to articulate information at different levels, depending on who’s sitting in front of us. So that automatically makes the message something that has to be tailored to something the patient can actually understand. The flip side is, even if we convey the information accurately and in a compassionate, understandable way, patients themselves put a value, depending on where they are in life, on what they are willing to accept. Some come to the conversation with as much information as the clinician, and others have nothing. These patients may be 60 years old, they don’t want to be sick, and they don’t want to think about anything else. Other patients want a 1% gain, if a 1% gain is available, at any cost. Each patient is unique, and the way the information is conveyed to each patient by the provider is also unique. This is something that would be very difficult to standardize.

Dr Schwartzberg: I think this is an education issue. Physicians are concerned about doing harm to the patient. When we have a patient with a large body surface area, it is human nature for us to want to hold back on the dose. Those of you who are in the business of developing systems can help, because now we have evidence that we should not dose-reduce. From a systems’ perspective, when physicians prescribe a dose that is less than what it should be, the system should communicate a message that says, “Dr Schwartzberg, are you sure?” It would also be helpful if the system could link to additional resources, particularly for physicians who are practicing in a small group practice, who may not have easy access to the data that support a treatment recommendation.

My other comment involves the integration of genetic testing into clinical practice. I still believe that we do not know how to integrate routine, high-quality, standard pathology measures with gene-extraction profiling and other related tools, especially when it comes to the equivocal results or the discordant results. For discordant results, there is still considerable uncertainty about what would be the best decision for that individual patient.

These genetic tests are trying to refine which patient populations are most likely to derive clinical benefit. As these tests evolve, we are becoming better at determining the high- and low-risk populations. But we are always going to be left with a small group in the middle, and there will not be an assay at this point that can truly tell us whether that patient should be treated. For these patients, it is going to be nearly impossible to predict, unless we conduct a randomized clinical trial, enrolling thousands of patients, to identify a 2% or 3% absolute difference between those 2 groups, with a very narrow confidence interval.

Dr Hiatt: Patient variability will be very difficult to determine and to standardize. Most patient behavioral and cultural variables are not controllable. When we look at subsets of patients who were not treated in accordance with an evidence-based algorithm, I suspect that uncontrollable patient variables are often a major factor.

Dr Hornberger: I have learned to trust that there is a moral decision made by most physicians with most patients, and 99% of the time, physicians will exercise sound clinical judgment. So I am not advocating that we take a Transportation Security Administration approach to medicine. The 1% of oncologists who are idiosyncratic and make questionable decisions need to be identified and punished in some legal way, but these individuals should not be driving the way we model and design healthcare.

I believe that if we conduct a chart review for the 10% of low-risk patients who are receiving chemotherapy, we will find that there was something idiosyncratic about that patient’s tumor that led the physician to err on the side of caution and recommend chemotherapy. That has just been my experience.

Dr Hiatt: Some of it is also driven by patients saying, “I don’t care if it’s a 1% chance of recurrence; I don’t want to take a chance.”

Dr Fortner: With regard to the clinical utility of genetic tests, we should ask the patient beforehand, “Are you absolutely going to take chemotherapy regardless of the test result?” The test is only useful if we act on it. We need to speak with the patient first, and have a probing conversation with him or her, then make a shared decision that incorporates the patient’s perspective.

Dr Wolff: We will never have 100% concordance with clinical practice guidelines, nor should we. If that were the case, we could have a computer practicing medicine. We are not going to have concordance above 90% or 95%, because there are always going to be extenuating circumstances, which could be valid and legitimate personal or biologic preferences, or issues that the test is not going to be able to detect. I don’t want to give the impression that if we are deviating from a guideline or a recommendation, then we are inherently wrong.

Dr Hornberger: Interpretation remains an important issue. The reporting of these tests varies. For some tests, it is just a dichotomous yes–no type of bracketing. In others, there are 3 brackets and a continuous score. As we move toward predictive assays, more tests are going to have a continuous scale. The FDA is concerned that without education, many doctors are not sophisticated enough to interpret the data properly. The FDA prefers simple
yes–no contingency tables. However, this type of data presentation is, in fact, artifactual to a degree. Within the low spectrum, there are high lows, low lows, and intermediate lows. Therefore, a continuous scale makes more sense from a presentation perspective. Although that is the right way to report it in an academic manner, in reality, we have to report the data in the real world, with people who are not always that sophisticated in these techniques. It creates some of these interpretive challenges.

**Dr Wolff:** I don’t think we should underestimate the ability of the user, a physician, or a patient to learn how to use and interpret genetic tests over time. That is one of the biggest challenges of transferring a technology from the research side to the clinical side. It is our job to develop tools to help that rather than just try to simplify and assume that they cannot deal with the information.

### The State of Community Oncology

Payment reductions instituted as a result of macroeconomic healthcare cost pressures threaten the viability of the community oncology business model. Drugs account for a large proportion of revenue in this sector; however, for many community oncologists, drug reimbursement is currently below the threshold required to maintain a profitable practice. In addition, it can be argued that community oncologists have not been effective in advocating for their profession. As a result of these factors, coupled with the fact that oncology remains profitable for hospitals, large numbers of community oncologists have left private practice in the past few years and have joined hospital-affiliated networks or academic medical centers. Because existing economic pressures are likely to continue, and even to intensify, it is difficult to see the trend abating unless new value-based payment models are implemented to compensate physicians fairly. The following discussion touches on the key issues faced by community oncology today and those that are likely to be faced in the future.

**Dr Fortner:** There is a fundamental ethical process taking place that is borne out by the fact that community oncologists continue to treat Medicare patients, even though it is unprofitable for them to do so. The sheer fact that they have continued to practice with these patients is a testament to the reality that they are tenaciously and ideologically driven to provide care. What we have seen over the past 36 months is a marker. I don’t believe that community oncology will shift to the point where the majority of care will be delivered in a hospital outpatient setting in the next 5 years.

However, we have seen enough movement in the hospital outpatient department setting that everyone now knows it is a real possibility. When care shifts to the hospital setting, the cost per infusion essentially doubles, because of the way the commercial insurer payment systems are constructed. The charges are part of a bundled hospital contract. That is one immediate implication of the shift.

There are also long-term access issues to consider. If the fiscal viability of a private practice is no longer sustainable, then our rural care will suffer. If 1 or 2 physician oncology practices in less populated areas are forced to close, there will be drug shortages in certain areas, and there will be an access crisis for patients.

**Dr Schwartzberg:** Your comments are very well taken, but they are not going to change the momentum. There already are access issues. Rural practices have closed. Some physicians have seen their incomes drop by one third. As business owners, some community oncologists don’t pay themselves; rather, they pay everyone else, and it is a tremendous burden for them to afford an inventory of expensive drugs. If a single dose of an expensive drug is not paid, it is $10,000 out of their pockets. So, they are looking for safe harbors, and you can understand why.

I don’t think the train has left the station, but we have already seen quite a shift in the past year. One year ago in Memphis, 100% of medical oncologists were in private practice. Today, 95% are either affiliated or were purchased by hospitals. The switch flicked overnight. The same dynamic is taking place in many other areas. I predict that in 5 years, 80% of community oncologists will either be a part of a large hospital-affiliated network or a part of an academic medical center. I believe that will be the landscape in the future. How are we going to deal with that?

**Dr Wolff:** As physicians, we want to do the right thing for our patients. However, when incentives are misaligned, it may take us down the wrong path. If things are broken, how do we fix them? Ultimately, as voters, is it not our responsibility to effect change?

**Dr Fortner:** Community oncology, during the good years, should have been implementing electronic medical records and developing world-class outcomes databases that were built on transparency. They did not, and as a result, they do not have the data needed to support their arguments. Furthermore, there are very negative stereotypes that developed regarding community oncology, and they have persisted. In fact, the Centers for Medicare & Medicaid Services (CMS) continues to talk about dropping payments further. There are macroeconomic pressures to save money, regardless of the potential consequences to patients and physicians. I do not believe that CMS is taking a rational approach to health policy with regard to oncology. As a result, the shift of care to the hospital setting is an unfortunate, unintended consequence. I will not argue that it is not going to happen; I will argue that it is a poignant shame.

**Dr Schwartzberg:** I would argue that we need to shift the discussion from “Is it going to happen or not?” to “How to make the best of it.”
Implications of Genomic Testing for Payers

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It has been difficult for payers to obtain adequate information from claims data to understand how genomic tests are being used clinically. The difficulty results from the claim codes being representative of the laboratory methods or individual analytes, and not the purpose of the test. These issues can be better appreciated if payers use claims data to help them understand if and when a test was performed, and then supplement this with medical information obtained from the ordering provider to understand adoption of new tests and practice variances in population medicine. To understand how test results are applied to individual patient care, payers can obtain preauthorization information from the ordering provider.

Payer interests vary according to the types and the uses of these tests. Payers do know that these tests can be used to confirm a clinical diagnosis; however, they cannot know from claims whether the appropriate medical and genetic histories have been obtained. In many instances, this information has not been documented nor have the histories been adequately obtained, and had this information been obtained, the test may not have been necessary.

When using these tests to inform treatment decisions or drug selection, payers can know when the test was performed, but not if and how the test results were used in medical decision-making, unless payers obtain the test results at the time of preauthorization for drug coverage. Genomic tests used to predict the likelihood of developing a particular disease (eg, breast cancer) invite the conversation of informed consent and shared decision-making. Payers have little knowledge regarding the extent to which informed consent and shared decision-making have been adequately performed.

In the case in which a test is used to decide whether to treat or to assist with drug selection, it is important for payers to understand that the member and the provider recognize the limitations of the test and how the test results might be used in rendering treatment decisions. This is not an easy task, given the fact that many clinicians are still learning how the tests fit algorithmically into decision-making. In addition, health literacy issues confound patients’ understanding and interpretation of risk. Assuming that members and are able to apply their understanding, they are better equipped to know the value of the test. For example, if the probability exists that a member might not benefit from chemotherapy, but there is still a slight chance of treatment benefit and the member wants to take that chance, that discussion and shared decision-making should take place prior to considering use of the test.

Health plans have an interest in making certain that such dialogue has taken place. There are also issues associated with clinician communication and integration. If it is appropriate to use a particular test, and the test is ordered but the treating physician is not made aware of the test results, there is little or no value derived from the test. Health plans are interested in making certain that test results end up in the decision makers’ hands in a timely fashion, and that they are interpreted and applied appropriately. It is in these areas of informed consent, communication, and provider education that payers can play a supportive role to ensure that these gaps are met.

In the introduction of tests new to market, payers have an interest in making certain that laboratory error is minimized, end-user education has been maximized, and tests are clinically valid to impact treatment decisions that improve health outcomes. Payers want to understand the design of clinical trials that will be used to bring companion diagnostics, as well as predictive tests that come to market, so that these tests are analytically and clinically validated. Because many of these tests are marketed directly to consumers or to clinicians, this governance of clinical utility is unlikely. Many of these types of tests are performed in sole-source laboratories or in environments in which there is little governance over laboratory quality and clinical utility. A variety of genomic tests remain under the category of Laboratory Developed Tests, with little understanding of laboratory quality standards. The US Food and Drug Administration has only recently issued draft guidance addressing genomic testing for clinical use (eg, companion diagnostics) in the approval process.

In an environment in which both providers and payers are considering innovative payment models that assign risk to providers, payers will be required to ensure that members receive quality testing from laboratories and that these tests are appropriately used. Expressed differently, payers will need to ensure that quality tests are made available to members in the appropriate clinical situations. In this environment, payers can also play a supportive role in continuing education, as well as knowledge management.

Author Disclosure Statement
Dr Loy is shareholder of Humana and Precision Therapeutics.

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