The rapid growth of biotechnology treatments experienced over the past 10 years has created a double-edged sword for managed care oncology stakeholders. While targeted therapies and biologics for the treatment of cancer in many cases offer an improvement over traditional chemotherapy in terms of improved efficacy and reduced toxicity, these drugs also carry an extraordinarily high price tag.

Whether they are used alone or in combination with conventional cytotoxic therapies, biologics have yielded improvements in treatment outcomes across many different cancers. In fact, these therapies have even become standard of care in their approved indications in many circumstances. The resulting high level of uptake, coupled with the premium prices of these agents, has made targeted therapies leading treatments in the oncology market in terms of sales. For example, global sales of targeted therapies grew an astonishing 33% in 2007, totaling $17.3 billion for the year.¹ These costs have, in turn, been a significant driver of the specialty drug trend in the U.S.; specialty drug spending increased 12.3% in 2007.² Considering that cancer treatments contributed 17.3% to this rising trend – third among all therapeutic classes – the impact of targeted therapies on plan spending is significant in managed care.²

In an effort to address the high cost of these novel biologic agents, managed care stakeholders have employed a number of pharmacy management methods that are often better suited for traditional prescription therapies. After exhausting these conventional
The burgeoning field of molecular diagnostics has added a new dynamic to the management of chemotherapy and the incorporation of pathways-based programs by managed care organizations (MCOs). Similar to targeted therapies themselves, molecular diagnostic tests offer the promise of improved quality of care, but at an apparent increased cost. The increased cost associated with molecular diagnostics, however, may be offset by the prognostic and predictive values of these assays, which allow for more clinically appropriate and individually tailored therapy than ever before. Furthermore, the application of molecular diagnostics will likely afford the decreased use of chemotherapy and supportive care and decreased efforts focused on the management of adverse reactions; this could potentially provide for cost offsets or even cost savings while attaining better quality of care for patients. This is particularly important when considering the price of these targeted therapies, which can cost up to $60,000 for agents such as cetuximab (Erbitux) in the treatment of colon cancer. Molecular diagnostics, which themselves can cost up to approximately $4,000 per test, can offset cost outlays in situations where a particular targeted agent will provide little or no therapeutic benefit. As such, these diagnostic tools may provide a valuable and evidence-based means of utilization management and risk stratification for therapies when coupled with the already proven clinical pathways programs being adopted by many MCOs for treatment regimens.

As overtreatment, has recently become more apparent in the management of certain cancers, including breast and colon. For example, while the benefits of tamoxifen and chemotherapy in women with node-negative, estrogen-receptor-positive (ER+) breast cancer have been extensively documented, the risk of distant recurrence in patients treated with tamoxifen alone after surgery is only approximately 15% at 10 years. This translates into ≥85% of the unneeded chemotherapy and supportive care. The ensuing improvements in consistency of care have led to increased quality, reduced episode of care costs, and decreased inappropriate use of costly therapies.

Utilization management techniques, payors have recently turned toward interventions designed to improve the practice of medicine, including the use of clinical practice guidelines, as a means of enhancing quality and controlling costs. The resulting improvements in patient care have demonstrated the cost utility of sound clinical practice and the value of evidence-based medicine over myopic cost-centered management measures. One such clinically based intervention is the incorporation of evidence-based pathways for the treatment of certain cancers. In provider networks (such as that of the University of Pittsburgh Medical Center [UPMC]), these pathways programs began as a means of controlling treatment variation and fostering evidence-based practices, subsequently yielding cost savings for payors (such as Highmark Blue Cross Blue Shield [BCBS], in the case of UPMC) in the process. Under the pathways protocol, participating UPMC oncologists are required to treat patients according to predetermined, evidence-based clinical pathways, thereby reducing treatment variation. The ensuing improvements in consistency of care have led to increased quality, reduced episode of care costs, and decreased inappropriate use of costly therapies.

### Table 1 Costs Associated with Cancer Care (2007 $U.S.)

<table>
<thead>
<tr>
<th>U.S. Data</th>
<th>Billions</th>
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<tbody>
<tr>
<td>Total Cost of Cancer 2007</td>
<td>$219</td>
</tr>
<tr>
<td>Direct Medical Costs</td>
<td>$89</td>
</tr>
<tr>
<td>Cost of Cancer Drugs 2007</td>
<td>$17.8</td>
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<tr>
<td>Cost of Top 10 Cancer Drugs 2007</td>
<td>$14</td>
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Establishing the Value of Molecular Diagnostics

Of the $219 billion total cost of cancer in 2007, $89 billion is attributed to direct medical costs, with a significant burden on indirect costs ($130 billion). Of these direct medical costs, $17.8 billion (20%) is the result of cancer drug costs, indicating that a sizable portion of oncology cost management efforts should be directed toward the effective management of drugs and the ensuing direct medical costs (Table 1). Administration of oncology therapies can result in adverse events, such as hospitalizations and toxicities, and result in the excessive use of supportive and palliative care. Furthermore, the use of these therapies is based on clinical studies where clinical absolute benefit is small and often marginalized even further when the toxicities (including death) of chemotherapy are factored into the equation, thereby demonstrating poor clinical cost utility for MCOs. Situations such as these – especially where supportive care is required due to the untoward effects of unnecessary chemotherapy – are prevalent in managed care oncology and contribute not only to rising drug costs but also to the rapidly escalating overall medical costs for cancer, which topped $89 billion in 2007 (Table 1). This phenomenon, known as overtreatment, has recently become more apparent in the management of certain cancers, including breast and colon. For example, while the benefits of tamoxifen and chemotherapy in women with node-negative, estrogen-receptor-positive (ER+) breast cancer have been extensively documented, the risk of distant recurrence in patients treated with tamoxifen alone after surgery is only approximately 15% at 10 years. This translates into ≥85% of...
patients receiving chemotherapy with minimal clinical benefit, assuming universal administration among women with the same breast cancer type. Furthermore, Fisher et al reported only a 4.4% mortality benefit in patients treated with tamoxifen plus chemotherapy versus tamoxifen alone among women with similar breast cancer characteristics. In light of this finding and market data indicating 60% chemotherapy usage in similar patients, current practice patterns indicate a 19-fold incidence of overtreatment in women with node-negative, ER+ breast cancer (Figure 1).

Similar instances of cytotoxic chemotherapy use with marginal therapeutic benefit likewise factor into the over-inflated total costs associated with the treatment of other cancers. Adjuvant chemotherapy appears to produce a small (1% to 5%) survival benefit for stage II colon cancer patients after median follow-up of 4.2 years; however, the risk-benefit of adjuvant chemotherapy is complex given the high toxicity rates from the fluorouracil/leucovorin (5-FU/LV) regimen. Data on 5-FU/LV in the treatment of stage II colon cancer suggested a mortality improvement of 2% to 4% absolute benefit in the Quick and Simple and Reliable (QUASAR) trial. Regarding fatal toxicities in the registration capcitabine trial for adjuvant therapy of stage III colon cancer, the safety data was reported separately. The incidence of toxic death with capcitabine was comparable to that seen with 5-FU/LV (0.3% vs. 0.4%) and the regimens were comparable for all-cause 60-day mortality (0.5% vs. 0.4%).

An unmet need for better prognostic molecular diagnostics to stratify risk of recurrence of stage II/III colon cancer among patients is apparent when small mortality benefits are weighed against the deaths attributable to toxic chemotherapy.

By providing prognostic information about a patient’s risk of disease progression and/or by predicting the clinical benefit of oncology therapies for specific patients, valid and reproducible molecular diagnostics serve to significantly reduce these instances of overtreatment, thereby optimizing the drug benefit in managed care oncology. In the treatment of colon cancer, another disease plagued by overtreatment, Kras genetic testing has already begun to yield economic returns. This particular test is currently employed to determine if epidermal growth-factor receptor (EGFR) inhibitors such as cetuximab should be prescribed, based on a patient’s genetic profile, since no clinical benefit is derived from treating patients who have mutant Kras gene expression with these costly targeted therapies. In a study by Shankaran et al, the use of Kras testing to prescribe cetuximab only to patients with wild-type Kras expression was estimated to result in $604 million in annual net savings inclusive of the cost of the test. This is not at all surprising in light of the 35.6% to 42.3% prevalence of Kras mutations for which cetuximab may be inappropriately prescribed without the predictive value of molecular diagnostics.

Favorable economic outcomes have also been reported in association with the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (Onco type DX) in node-negative, ER+ breast cancer. This assay, which predicts distant recurrence-free survival by assigning a recurrence score (RS), allows for more individually tailored therapy that is less aggressive (i.e., hormonal therapy alone) when the risk of recurrence is low. In an economic analysis by Hornberger et al demonstrating the cost utility and cost effectiveness of Onco type DX, the RS derived from the assay in node-negative, ER+ early-stage breast cancer was predicted on average to increase quality adjusted survival by 8.6 years and reduce overall costs by $202,828 in a modeled cohort of 100 women. Researchers from University of Pittsburgh Cancer Institute likewise

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**Figure 1**

Overtreatment Disparity Between Current Practice and Clinical Benefit for Adjuvant Chemotherapy in Node-Negative, ER+ Early-Stage Breast Cancer
reported cost savings associated with Onco
type DX in a cohort of 260 women with node-negative, ER+
invasive breast cancer. In this study, cost savings associated with selective adjuvant chemotherapy using Onco
type DX were estimated to be $920,000. Analyses such as these have led to a shifting paradigm in managed care oncology in which proven molecular diagnostic tools have experienced increased use and payor uptake. This is partly due to numerous endorsements by professional organizations such as the American Society of Clinical Oncologists (ASCO) and the National Comprehensive Cancer Network (NCCN), which have recognized the value of these clinical interventions. Kras testing for EGFR-inhibitor therapy in colon cancer is endorsed by both ASCO and NCCN in various practice guidelines and treatment algorithms, including NCCN’s Clinical Practice Guidelines in Oncology. In addition, the use of genetic markers with prognostic and predictive value for breast cancer is also cited by both organizations as being sound clinical practice. ASCO’s 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer cites a number of new categories as showing evidence of clinical utility and recommends these markers for use in practice (Table 2). These recommendations were made based on the available data supporting the validity and clinical utility of the specific markers, which has been robust to date. In fact, in the document, ASCO cited the data supporting Onco
type DX – the only recommended multiparameter gene expression assay endorsed by the organization – as being Category Level I. In addition to these recommendations, ASCO and the College of American Pathologists (CAP) collaborated to develop guideline recommendations for HER-2 testing in breast cancer, which recommends strategies to improve HER-2 testing accuracy for enhanced clinical decision making. Other published documents, such as NCCN’s Genetic/Familial High-Risk Assessment: Breast and Ovarian, recommend the use of genetic analyses to determine cancer risk in women with specific markers like BRCA1/BRCA2. With an expanding collection of clinical evidence supporting the use of specific molecular diagnostic tests and their accompanying endorsement by professional oncology organizations, the uptake of these predictive and/or prognostic tools by MCOs seems intuitive. However, before such interventions can be adopted by payors and incorporated into quality improvement and utilization management initiatives such as clinical pathways, they must be thoroughly evaluated. This evaluation should be based first and foremost on three criteria for molecular diagnostic tests, defined as follows:

- **Analytical validity** – The ability of a test to produce consistent results (i.e., reproducibility)
- **Clinical validity** – The ability of a test to accurately predict outcomes, such as risk of recurrence and/or predict response to treatment
- **Clinical utility** – Including risk reclassification, or the percentage of patients in which the test reclassifies disease recurrence risk; change in therapeutic choice, or the percentage of patients in which treatment is altered due to the results of the test; and improved patient outcomes, which is simply the effect of test results on patient outcomes

Once a molecular diagnostic test has met these three criteria, the economic validity and implications, such as the costs and cost effectiveness, may be reviewed and evaluated. As with the evaluation of drug therapies, this latter economic criterion should be considered only after the medical value has been established using the first three criteria.

Applying a comprehensive evaluation process such as this in a consistent manner can present a significant challenge in managed care, where universally accepted protocols for the evaluation of diagnostic tests represent relatively uncharted territory. This becomes increasingly apparent when considering the initial criteria being applied in the fledgling regulatory

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**Table 2** New Categories of Tumor Markers Showing Evidence of Clinical Utility in Breast Cancer Endorsed in ASCO’s 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

<table>
<thead>
<tr>
<th>Tumor Marker</th>
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<tr>
<td>CA 15-3</td>
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<tr>
<td>CA 27.29</td>
</tr>
<tr>
<td>Carcinoembryonic antigen</td>
</tr>
<tr>
<td>Estrogen receptor</td>
</tr>
<tr>
<td>Progesterone receptor</td>
</tr>
<tr>
<td>Human epidermal growth factor receptor 2</td>
</tr>
<tr>
<td>Urokinase plasminogen activator</td>
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<tr>
<td>Plasminogen activator inhibitor 1</td>
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<tr>
<td>Certain multiparameter gene expression assays</td>
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pathway for molecular diagnostics, which are different from the standards used to evaluate drugs and biologics and still being debated at this stage in their development.

**Incorporating Molecular Diagnostics in Managed Care**

Although the value of certain molecular diagnostic tests (e.g., *Kras* testing and *OncoType DX*) has been established to the point of widespread coverage (*OncoType DX* is covered for >90% of insured lives in the U.S.) and incorporation into treatment protocols by many MCOs, other recently introduced tests require careful evaluation. Similar to the evaluation of recently introduced drug therapies, payors should assess the value of these new diagnostic tests primarily on their clinical merits and medical utility as determined by published literature and provider input. However, the evaluation of recently introduced molecular diagnostics diverges from that of drug therapies in that efficacy and safety are valid primary endpoints for drugs and biologics, while the evaluation of diagnostics requires application of the specialized criteria outlined previously. Furthermore, whereas published literature serves as the primary source of information used by payors in evaluating drug therapies, there is often little published peer-reviewed data available that document the clinical merits of molecular diagnostics. Similar to the evaluation of recently introduced drug therapies, payors should assess the value of these new diagnostic tests primarily on their clinical merits and medical utility as determined by published literature and provider input. However, the evaluation of recently introduced molecular diagnostics diverges from that of drug therapies in that efficacy and safety are valid primary endpoints for drugs and biologics, while the evaluation of diagnostics requires application of the specialized criteria outlined previously. Furthermore, whereas published literature serves as the primary source of information used by payors in evaluating drug therapies, there is often little published peer-reviewed data available that document the clinical merits of molecular diagnostics.

One test that has been surrounded by significant controversy due to its limited supporting data is the OvaSure test, introduced to the market by LabCorp in late June 2008. While the need for such a test is significant, the FDA deemed OvaSure as having unfit data to support its use in the U.S. in August 2008. The test, which measures the levels of six proteins, correctly classified 221 of 224 blood samples taken from women with ovarian cancer or controls. While this 95% accuracy rate in detecting ovarian cancer and the 0.6% false-positive rate are impressive, the agency cited several issues for not supporting the test, primarily associated with the adequacy of the data. Among these were that the single study validating the accuracy of OvaSure was the only study to do so, and that the testing was not independent of the manufacturer. Conversely, molecular diagnostic tests that have experienced robust uptake by payors, such as *Kras* testing and *OncoType DX*, are often supported by a number of independent studies and guidelines that provide the necessary evidence to make a determination of significant medical utility.

Once a molecular diagnostic test has been deemed as having medical utility worthy of incorporation into payor treatment protocols or drug medical policy, managed care stakeholders must make a decision as to how the test will be utilized to drive the appropriate treatment. Prior authorization (PA) is an option available to payors as a means of requiring that providers perform the necessary diagnostic tests when appropriate for some therapies. This means of incorporation of molecular diagnostics can be applied to predictive diagnostic tests for targeted agents such as trastuzumab (Herceptin), which has an FDA-approved label mandating the use of HER-2 testing prior to initiation of therapy. Oftentimes, these PA requirements are lifted after a diagnostic test is on the market for a sufficient length of time and utilization review can document appropriate use of a targeted therapy being driven by the test. While PA may be used effectively to this end, one challenge that may arise from employing this method to mandate the use of molecular diagnostics for corresponding therapies is that varying codes currently exist to represent these tests. As such, it may be difficult to interpret the use of molecular diagnostics as a means of utilization management and to retrospectively quantify test use from claims data. Another potential challenge with PA is that this utilization management tool may be viewed as a burden or obstacle by providers and may ultimately discourage the use of targeted agents coupled with diagnostic tests – a clear conflict from obtaining the needed behavior change and benefit that stems from use of molecular diagnostics.

One final challenge that may be encountered when employing PA as a means of incorporation of molecular diagnostics is that not all tests are coupled with agents to determine drug responsiveness.
in the same manner as HER-2 is to trastuzumab or Kras is to cetuximab. In these cases, local oncology standard practices must be taken into consideration before utilizing PA if appropriate treatment choices stemming from the incorporation of molecular diagnostics could be hampered.

Some organizations such as UPMC have incorporated the use of molecular diagnostic tests into evidence-based clinical pathways and thereby mandate their use as part of a uniform and standardized treatment protocol. This form of incorporation parallels the role that molecular diagnostics plays in a number of NCCN treatment algorithms, where a specific result on the appropriate test is described as a necessary step before selecting a particular therapy. By guiding treatment in this stepwise manner, the incorporation of molecular diagnostics into evidence-based clinical pathways eliminates the need for PA to drive the appropriate use of these tests. The appropriate patients are given the appropriate tests, and the results dictate the appropriate treatment decision, all according to evidence-based pathways protocols.

The process employed for incorporating molecular diagnostics into evidence-based clinical pathways in managed care is perhaps best demonstrated by the practices of the UPMC provider network and its payor Highmark BCBS, the first collective managed care entity to implement such an intervention on such a scale. When considering coverage for a newly available molecular diagnostic test and the eventual inclusion of the test in a clinical pathway at UPMC, Highmark BCBS management approaches physicians within UPMC to solicit clinician opinion on the test’s validity, utility, and overall value. The physicians, in turn, research the available data associated with the test, as well as the inclusion of the test in existing clinical practice guidelines or recommendations published by professional organizations, and draw from clinical experience when applicable in order to form an educated and evidence-based opinion. In this manner, certain UPMC physicians serve as consultants to the payor, offering advice in their areas of expertise and based on a thorough review of the pertinent literature. Following the recommendations of the UPMC physicians, Highmark BCBS management either writes medical policy enacting coverage for the diagnostic test or forgoes coverage altogether, depending on the consensus of the consulting physicians.

The same data and often the same physicians involved in consulting on coverage determinations for the test are next taken to the regular quarterly meeting of the appropriate pathways committee, based on the type of cancer in which the particular diagnostic test is used. The academic chair of the committee may also call an unscheduled meeting if he or she feels it best to review inclusion of the test immediately due to an urgent medical need. If the committee decides to include the test in the pathway, the committee members then discuss the appropriate role of the diagnostic test within the pathway, including the manner in which it will be incorporated into the pathway. Following the decision for inclusion, notification is sent out to the appropriate members of the provider network, making them aware of the changes made to the pathway and the date on which this change will be enacted in clinical practice. Use of the test becomes an active component of the pathways protocol once all of the necessary administrative and information technology (IT) measures associated with the change are complete.

In this manner, Highmark/UPMC has incorporated a number of proven molecular diagnostic tests into their innovative pathways program, including Kras testing and Oncotype DX. Kras testing is a necessary step in the colon cancer pathway prior to the prescription of cetuximab for colon cancer. Use of the Oncotype DX assay is required as part of the breast cancer pathway prior to prescribing adjuvant therapy in women with node-negative, ER+ invasive breast cancer who are candidates for chemotherapy. Based on the results of the assay, pathways patients with a RS<18 are indicated to receive tamoxifen therapy alone, while patients with a RS>18 are indicated to receive tamoxifen therapy in addition to adjuvant chemotherapy.

In light of recent data, the role of Oncotype DX in the breast cancer treatment pathway at Highmark/UPMC is also being considered for expansion to include guidance for adjuvant chemotherapy treatment decisions in patients with micrometastases (i.e., metastases <2 mm in size). Although current diagnostic practice includes a detailed histologic examination of sentinel lymph nodes allowing for the detection of these microscopic growths, the determination of best practices is complicated by the fact that lymph nodes with micrometastases are not considered positive for the purpose of treatment recommendations. As such, Oncotype DX is under review by Highmark/UPMC for pathways inclusion for patients with node-
positive or pN1mi (micrometastasis: 0.2 to 2.0 mm), hormone-receptor-positive, HER-2-negative tumors, in accordance with updated recommendations in NCCN’s clinical practice guidelines for breast cancer. The use of Oncotype DX has also been recommended for determining the appropriate course of treatment in micrometastatic disease in the BCBS TEC Assessment.

Conclusion

The future of managed care oncology lies in optimal therapy derived from combining the merits of evidence-based prescribing and personalized medicine. While research and development drives the introduction of a new crop of increasingly effective therapies every year, these novel agents as well as established regimens do not provide the same level of medical benefit for every patient. This presents a quandary for managed care stakeholders, who are charged with the task of preventing the inappropriate use of these costly agents in patients for whom they will lend no clinical advantage. Molecular diagnostics represent a key component of the solution, allowing for individually tailored therapy among the diverse plan populations in managed care. Although these tests carry an additional cost, they are also highly predictive and supported by documented cost utility and cost effectiveness in many cases. Furthermore, when coupled with the evidence-based prescribing and logical, stepwise treatment driven by increasingly popular clinical pathways programs, molecular diagnostics offer even greater promise in optimizing therapy and minimizing the inefficient use of managed care resources.

Proven diagnostics based on a suite of clinical studies, such as *Kras* testing and Oncotype DX, provide a sound argument for the inclusion of molecular testing in coverage determination discussions, as well as for their incorporation in clinical pathways initiatives. In fact, extensively validated and well-defined tests such as these provide the perfect complement to systematic and evidence-based treatment protocols. Looking forward, the discovery and development of novel markers and diagnostics will serve to bolster the benefits of these combined interventions to an even greater degree, fueled by the introduction of additional assays to define better treatment decisions across multiple tumor types, such as renal cell, colon, and prostate cancers. While these new molecular diagnostics may offer potential promise in improving outcomes and reducing costs, it is critical for managed care stakeholders to apply the same rigorous evidence-based standards employed in the evaluation of recently introduced drug therapies. However, as opposed to considerations on safety and efficacy found in drugs and biologics, novel diagnostic tests must be assessed in terms of their analytical validity, clinical validity, and clinical utility, followed by economic validity once the first three criteria have been established. This manner of thorough evaluation will ensure that a considerable investment in molecular diagnostics is met with considerable returns.

References