Staging Colon Cancer: New Directions and Managed Care Implications

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ABSTRACT

Objective: In September 2009, the Pharmacy & Therapeutics Society gathered a study group of 12 managed care medical and pharmacy directors to examine the impact of biomarker-based assays on payers' ability to manage the cost and quality of cancer care.

Context: Colon cancer is expected to recur in approximately 30% of stage I and II patients. Only 4% of these patients benefit from chemotherapy. Being able to better identify those patients who are most likely to experience a recurrence and can benefit from chemotherapy can help improve the quality and reduce the cost of care.

Methods: To stimulate thought and discussion, the study group examined a particular biomarker-based assay, Previstage GCC (guanylyl cyclase C), and its potential impact on the management of colon cancer.

Results: The group agreed that biomarker-based assays can be used to more accurately determine which patients will most likely benefit from further diagnostic tests and/or chemotherapy, and which patients will not. Therefore, physicians and patients will be able to make better treatment decisions with this added information.

Conclusions: A significant number of new cancer therapies are expected to come to market in the next few years. Many of them are expected to be costly. The potential for significant growth in cost can only amplify managed care's interest in biomarker-based assays.

(Am J Pharm Benefits. 2010;2(1):21-28)

In September 2009, the Pharmacy & Therapeutics Society gathered a study group of 12 managed care medical and pharmacy directors. The objective was to examine the impact that biomarker-based assays could have on the approaches payers and providers use to manage cancer.

The study group's members represent a variety of commercial, Medicare, and Medicaid health plans and 1 integrated health delivery system. The health plans are located across the United States and cover more than 35 million lives. Each of the payer representatives was responsible for developing coverage policies for diagnostic assays. The variety of study group members ensured a breadth of perspective and a base of knowledge for assessing the potential impact of biomarker-based assays on the management of cancers.

Influence of Biomarker-Based Assays on Oncology Management

The vast majority of managed care advisers are intrigued with the possibilities offered by personalizing the treatment of cancers based on biomarker-based assays. Such medical advances offer an opportunity to optimize the multidisciplinary approach to care, improve outcomes, decrease the cost of care, and improve outcomes and quality of life for patients with cancer.

The study group found that although biomarkers offer potentially powerful data, their practical applications have yet to be thoroughly demonstrated in the medical community. For these assays to be of value, physicians should be able to use them to identify patients most appropriate for chemotherapy and vigilant care management and, perhaps more importantly, patients *not* likely to benefit from particular treatments and closer observation and management. Physicians must become more comfortable with deciding not to provide a particular treatment based on a biomarker-based assay, as well as confident that a particular treatment could be highly effective. In other words, they must become confident that relying on a biomarker-based assay would not generate an unacceptable level of clinical risk for the patient, nor create a legal liability or negative financial impact for the physician.

Author affiliations and disclosures provided at the end of the text.

Practical Implications

The Pharmacy & Therapeutics Society gathered a study group to examine a particular biomarker-based assay, Previstage GCC (guanylyl cyclase C), and its potential impact on colon cancer management.

- Biomarker-based assays may enable providers to better determine the type of care that is appropriate for patients with colon cancer, especially stage II patients.
- It would be reasonable for payers to encourage the use of Previstage GCC if it correctly indicates potential response to adjuvant chemotherapy for a high percentage of patients.
- Additional data are needed to risk-stratify the target patient populations and document the clinical and economic benefits afforded by the assay.

An Example: Colon Cancer

To better explore managed care's perspective on biomarker-based assays, the study group considered Previstage GCC (guanylyl cyclase C), a new assay for colon cancer. Approximately 145,000 new cases of colon cancer are diagnosed each year in the United States. Up to 80% of these patients present spontaneously with no family history of the disease. Among the total number of cases of colon cancer, 20% present as metastatic disease.

Colon cancer is the third most common type of non–skin cancer and the second leading cause of cancer-related deaths in the United States. That figure is staggering when considering the extent to which the disease is potentially curable if diagnosed and managed in its early stages.

According to the American Cancer Society, the 5-year survival rate is 90% for people whose colon cancer is found and treated at an early stage.[1] Because many people are not tested, only 39% of colon cancers are found at an early stage. Once the cancer has spread to nearby organs or lymph nodes, the 5-year survival rate decreases to 68%. For people whose colon cancer has spread to distant parts of the body, such as the liver or lungs, the 5-year survival rate drops further to approximately 10%. In 2008, nearly 50,000 people died from colon cancer.

The American Joint Committee on Cancer developed a classification system for staging colon cancer, the TNM classification system (**Table**). For example, a stage II colon cancer has grown into the colon tissue but has not spread to nearby lymph nodes and shows no sign of distant metastases. If the same patient had cancer cells in the lymph nodes, he or she would be classified as having stage III colon cancer. Up to 30% of patients with colon cancer are in stage I. Another 25% to 30% of patients with colon cancer are in stage II.[2]

Colon cancer staging is important because it determines the course of treatment. Generally, guidelines do not call for adjuvant chemotherapy in patients with stage I colon cancer. Adjuvant chemotherapy is suggested for patients with stage III colon cancer.

However, studies indicate recurrence in up to 30% of patients with stage I and stage II (pN0) colon cancer (patients are those whose lymph nodes do not show any indication of colon cancer [ie, node-negative patients]). Approximately 10% of patients with stage I and 20% of patients with stage II die of local or distant disease.[3] In response, physicians are treating up to 49.5% of patients with stage II with chemotherapy but with negligible benefit for many.[4] Data indicate that the absolute improvement in survival for patients with stage II receiving chemotherapy is 3.6%.

Today, it is unclear which patients with stage II colon cancer are likely to benefit from chemotherapy. As a result, almost all younger patients with colon cancer receive chemotherapy. Older patients weigh the risks and benefits of initiating chemotherapy. Some of them do not pursue it.

Managed Care and Colon Cancer

Almost all study group members suggest that colon cancer is not among managed care's highest priorities. The cost of managing a colon cancer population is not as significant as that for more prevalent conditions, such as asthma or diabetes. Also, many patients can be "cured" of colon cancer through the effective use of surgery and adjuvant therapy if caught early enough.

As colon cancer is not among insurers' highest priorities, most payers today do not tightly manage colon cancer. Payers tend to leave the approach to care for colon cancer to physician and patient discretion.

However, payers recognize the potential for improving the quality of care and outcomes for patients with colon cancer. Health plans have an interest in increasing survival and reducing recurrences, thereby reducing the potentially significant cost of treating colon cancer. The costs associated with positron emission tomography scans, computed axial tomography (CAT) scans, and chemotherapy are significant. These costs are likely to increase in the near future, especially because of the extensive pipeline of potentially more expensive cancer drugs.

The cost of care for patients with colon cancer can be better managed. For example, given that 3.6% of patients with stage II benefit from treatment with adjuvant chemotherapy, approximately 28 patients must be treated with adjuvant chemotherapy for 1 patient to realize benefit (ie,

number needed to treat = 28). The "wasted cost" of treating 27 patients with stage II colon cancer without clinical benefit is significant for payers.

There is no current consensus within the physician community regarding which patients with colon cancer should receive adjuvant chemotherapy. For example, the American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines are somewhat different as to which patients with colon cancer are appropriate for adjuvant chemotherapy. Managed care does not enforce compliance with either of these guidelines. This leads to variance in care, with some approaches being more aggressive than others. There are insufficient data to determine whether one approach is potentially more cost-effective than others. Standardization of approaches to care presents another opportunity to better manage costs and to determine which treatment protocols offer the best chance for prolonged survival or cure.

Table. TNM Classification System for Colon Cancer

Stage	T (Size and Depth of Tumor)	N (Lymph Nodes Carrying Cancer Cells)	M (Distant Metastases)
I	Invaded the muscular layer of the colon	None	None
II	Grew into the colon wall	None	None
III	Any size and depth	1 or more	None
IV	Any size and depth	Any number	Yes

Previstage GCC

Faced with a significant cost of care for individual patients suffering from colon cancer and uncertainties about the value of adjuvant chemotherapy in general, most payers support advances in care that have the potential to reduce that financial burden while maintaining or improving the quality of outcomes. Biomarker-based assays potentially represent such an advance.

As an example, the working group explored Previstage GCC. Previstage GCC is a new molecular test for the staging of patients with colon cancer. Staging a patient with colon cancer is important because it guides the physician's and patient's treatment decisions after the surgery.

Traditionally, physicians have relied on a blood test, scheduled at regular intervals, to measure levels of a protein called carcinoembryonic antigen (CEA). However, CEA is limited as a marker for colon cancer, detecting fewer than 60% of recurrent tumors.[5] It also has a high false-positive rate and is influenced by some nonmalignant conditions, such as cirrhosis, ulcerative colitis, and smoking. In addition, elevated CEA is associated with several cancers other than that of the colon, such as those of the breast, pancreas, and bladder.

Instead, Previstage GCC examines the entire portion of the lymph node submitted (whole or half node) and utilizes a molecular technique (quantitative reverse transcription polymerase chain reaction [RT-PCR]) to detect and measure the amount of GCC mRNA, a biomarker for colon cancer, in the lymph node.

Guanylyl Cyclase C and Diagnosis and Management of Colon Cancer

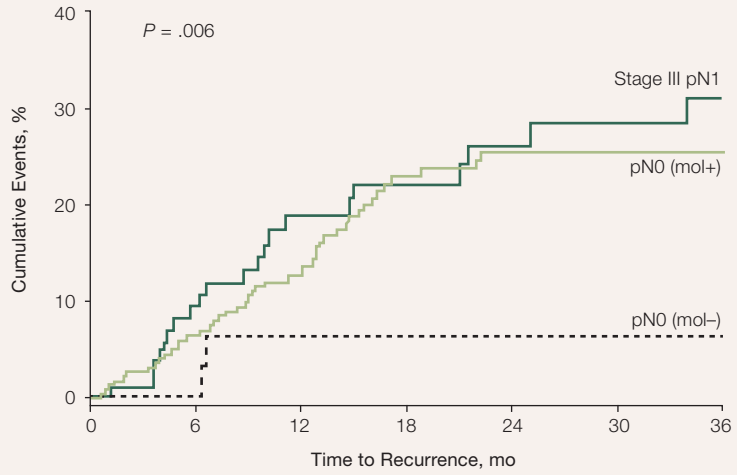
Studies have indicated that the presence of GCC in the blood may be an early indicator of micrometastases that would otherwise escape detection by the current standard methods of monitoring. Earlier detection provides an opportunity for immediate treatment to potentially improve patient outcomes and survival rates. Regular surveillance over a 5-year period is critical because colon cancer has a recurrence rate of 50%.[6]

Improved methods for predicting the recurrence of colon cancer could help identify patients who would benefit from adjuvant chemotherapy. Waldman et al[7] determined that GCC identifies occult metastases in lymph nodes that independently predict time to recurrence in patients with colon cancer. Thus, GCC may serve as a prognostic and predictive marker, identifying patients at minimum risk for disease recurrence and, conversely, those who might benefit from adjuvant chemotherapy.

More specifically, the Waldman et al[7] study showed that GCC expression, presumably indicating the presence of occult metastases, was detected in at least 1 lymph node from 225 patients (87.5%) with pN0 colon cancer. With a median follow-up time of 24.0 months (range, 1.8-62.7 months) for patients with pN0 (mol+) and 35.9 months (range, 2.5-62.1 months) for patients with pN0 (mol–), 20.9% (95% confidence interval [CI] = 15.8%, 26.8%) of patients with occult metastases, but only 6.3% (95% CI = 0.8%, 20.8%) of patients without occult metastases, developed recurrent disease (P = .006; **Figure 1**). Patients exhibited the well-established direct relationships between time to recurrence, disease-free survival, and disease stage.

Both patients negative for GCC who developed recurrent disease provided 2 or fewer lymph nodes for analysis

Figure 1. Time to Recurrence in Patients With pN0 Colorectal Cancer Stratified by Occult Lymph Node Metastases[a]



No. at risk							
Stage III pN1	87	75	54	44	35	26	25
pN0 (mol+)	225	195	157	102	80	57	53
pN0 (mol–)	32	31	28	24	21	19	13
Cumulative events							
Stage III pN1	0	8	15	17	19	20	20
pN0 (mol+)	0	15	27	42	45	45	45
pN0 (mol–)	0	0	2	2	2	2	2

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by quantitative RT-PCR, perhaps reflecting the requirement of any staging technique for adequate lymph node sampling (Figure 1).

The analysis by Waldman et al[7] revealed that grade, tumor location, lymphovascular invasion, therapy, and total number of lymph nodes harvested contributed little as prognostic factors in this cohort of patients with pN0 colon cancer. T stage also was a weak prognostic variable, reflecting the disproportionate number of T3 tumors (52.9%) compared to T4 tumors (7.4%) in the pN0 colon cancer cohort and the established relationship between tumor size, depth of penetration, and prognosis. However, GCC expression in lymph nodes provided independent prognostic information. As shown in **Figure 2**, patients with pN0 (mol+) exhibited earlier time to recurrence and reduced disease-free survival.

Waldman et al[7] illustrated that GCC is an advance in diagnostics compared to pathologic evaluation of patients whose lymph nodes do not show any indication of colon cancer (ie, node-negative patients). Patients found to be GCC positive are at risk of recurrence despite pathology reports showing them as node negative.

Waldman et al[7] showed that 87.5% of patients with colorectal cancer had lymph nodes positive for the GCC mRNA molecule.[7] Therefore, risk stratification data are required above and beyond determining that the patient is GCC positive. With risk stratification data, Previstage GCC potentially helps distinguish the patients with stage II colon cancer most likely to benefit from adjuvant chemotherapy from those least likely to benefit.

Importantly, factors other than risk stratification data, such as a patient's stage of colon cancer (eg, stage III), age, and comorbidities, could affect the decision to administer adjuvant chemotherapy. In addition, a study by Quah et al[8] found that 3 independent features significantly affected disease-specific survival: (1) tumor stage T4 (hazard ratio [HR] = 2.7; 95% CI = 1.1, 6.2; P=.02); (2) preoperative CEA >5 ng/mL (HR = 2.1; 95% CI = 1.1, 4.1; P = .02); and (3) presence of lymphovascular or perineural invasion (HR = 2.1; 95% CI = 1, 4.4; P = .04).[8]

Five-year disease-specific survival for patients without any of the above poor prognostic features was 95%; 5-year disease-specific survival for patients with 1 of these poor prognostic features was 85%; and 5-year disease-specific survival for patients with ≥2 poor prognostic features was 57%.[8]

Therefore, physicians should consider Previstage GCC's results together with all other available data before making a treatment decision for a specific patient.

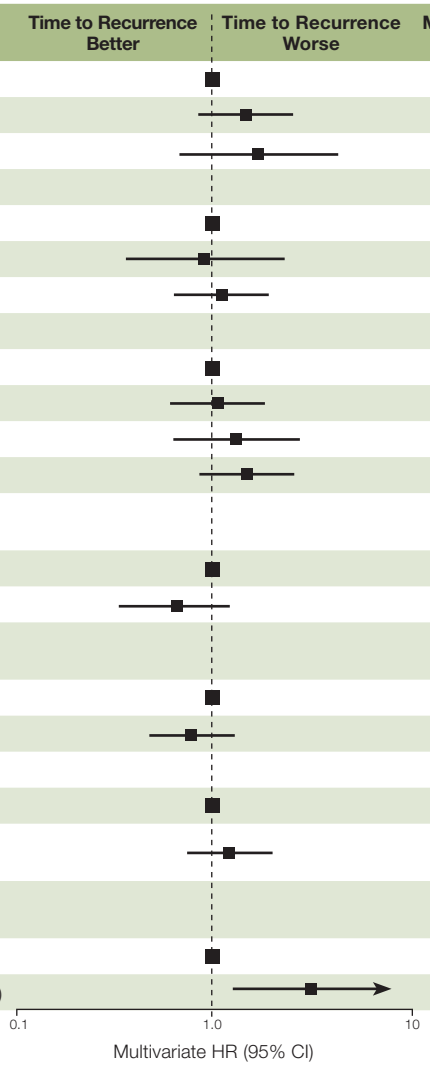
As with any new diagnostic assay, physicians and payers are concerned about undertreatment of patients (ie, not treating those patients who should have received adjuvant chemotherapy). Undertreatment of patients may reduce the quality of outcomes and raise issues of legal liability for physicians. These concerns are potential barriers to the adoption of Previstage GCC. Managed care also is concerned with the unnecessary financial and personal burden associated with overtreating those patients who are not likely to have a recurrence of the colon cancer.

Coverage of Previstage GCC

Managed care has limited experience developing coverage and reimbursement policies for biomarker-based assays. The study group identified other biomarker-based assays comparable to Previstage GCC with respect to

Figure 2. Cox Proportional Hazards Analysis of Time to Recurrence in Patients With pN0 Colorectal Cancer Undergoing Molecular Staging[a]

T Stage	No. of Events	No. of Patients	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	Multivariate *P*
1/2	14	102	1 [Reference]		1 [Reference]	
3	31	136	1.73 (0.92-3.25)	.09	1.75 (0.89-3.43)	.11
4	4	19	1.64 (0.54-4.99)	.38	2.35 (0.67-8.28)	.19
Grade						
Poor/unknown	5	40	1 [Reference]		1 [Reference]	
Well	3	19	1.54 (0.61-3.89)	.37	0.86 (0.20-3.74)	.84
Moderate	41	198	1.07 (0.25-4.46)	.93	1.10 (0.42-2.86)	.85
Location						
Rectal	6	35	1 [Reference]		1 [Reference]	
Right	17	108	0.95 (0.38-2.42)	.92	1.09 (0.40-3.03)	.86
Left	4	17	1.63 (0.46-5.80)	.45	1.52 (0.40-5.86)	.54
Sigmoid	22	97	1.55 (0.63-3.83)	.34	1.81 (0.71-4.60)	.22
Lymphovascular invasion						
No	43	204	1 [Reference]		1 [Reference]	
Yes	6	53	0.67 (0.28-1.57)	.36	0.51 (0.20-1.32)	.17
No. of lymph nodes harvested						
<12	13	45	1 [Reference]		1 [Reference]	
≥12	36	212	1.30 (0.70-2.41)	.42	0.61 (0.31-1.21)	.16
Treatment						
Surgery	35	200	1 [Reference]		1 [Reference]	
Surgery and chemotherapy	14	57	0.58 (0.31-1.09)	.09	1.22 (0.61-2.41)	.57
Occult metastases						
pN0 (mol–)	2	32	1 [Reference]		1 [Reference]	
pN0 (mol+)	47	225	4.09 (0.99-16.85)	.05	4.66 (1.11-19.57)	.04



CI indicates confidence interval; HR, hazard ratio.
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coverage and reimbursement issues. An example is Oncotype DX, which is a diagnostic tool marketed by Genomic Health for the management of breast cancer. Thus, the precedent exists for coverage of such biomarker-based assays under the appropriate conditions.

Ongoing research and analysis could identify cutoff points for GCC cell presence that would be much stronger predictors of the probability of disease recurrence and the expected benefit of adjuvant chemotherapy, either in general or with respect to a specific therapy. Such data could lead to changes in the treatment pathway for node-negative patients. Similarly, such research could potentially identify patients who, although GCC positive, have sufficiently low levels of GCC that its presence would not be considered a clinically relevant finding.

Managed care would find Previstage GCC's risk stratification data compelling if it yielded 3 categories of patients: (1) no need for adjuvant chemotherapy (approximately 1 of 5 patients with stage II colon cancer are expected to fall into this category); (2) likelihood of beneficial results from adjuvant chemotherapy (approximately 1 of 4 or 5 patients with stage II colon cancer); and (3) further evaluation appropriate (more than 50% of the patients with stage II colon cancer).

The study group agreed that payers are most interested in the first group of patients: those who are not likely to benefit from adjuvant chemotherapy. Eliminating the administration of costly therapy for those not likely to benefit would reduce the cost of care and avoid the risks associated with chemotherapy while leaving ultimate outcomes unaffected for this group of patients with stage II colon cancer.

The next patient group of greatest interest to managed care are those in the third category. Without Previstage GCC, many of these patients would be treated with adjuvant chemotherapy, perhaps unnecessarily. Previstage GCC might enable oncologists to safely delay the administration of chemotherapy for these patients and observe how their condition progresses. Chemotherapy would be administered only if there was a concern about the recurrence of colon cancer. The Waldman et al[7] study was not intended to identify the data cutoff points for these 3 groups. Further research by Waldman's group and by DiagnoCure, the marketer of Previstage GCC, is intended to address this issue.

If Previstage GCC provides diagnostic data that show the risk of recurrence is so low that adjuvant chemotherapy does not need to be administered, then plans will have a compelling value proposition for covering Previstage GCC. Other reasons for coverage would be the reduction in the morbidity associated with unnecessary chemotherapy. The impact of assays, such as Previstage GCC, on the cost of care and the clarity of the patient segmentation afforded by the GCC biomarker has to be credible and well defined. Data must demonstrate the value of GCC as an additional risk factor for the recurrence of colon cancer. It would be reasonable for payers to cover Previstage GCC if it correctly indicates potential response to adjuvant chemotherapy for a high percentage of patients.

Previstage GCC can reduce costs other than that of adjuvant chemotherapy. For example, the study group reflected on the possibility that Previstage GCC may replace the histopathology portion of the process for patients in certain circumstances. These cost savings will further encourage coverage of Previstage GCC. However, even in the current environment, having data on the GCC status of node-negative patients can help inform decisions regarding adjuvant chemotherapy when considered in conjunction with other risk factors.

The cost of chemotherapy is increasing, and many chemotherapy drugs and biologics under development are expected to be more costly than current chemotherapy agents. Therefore, the potential cost savings Previstage GCC offers by reducing the administration of adjuvant chemotherapy for patients not likely to benefit from it are expected to become more important in the near future. The greater Previstage GCC's potential for cost savings, the more likely managed care will provide coverage.

After gaining more experience with Previstage GCC over some period of time, health plans may review their data and determine that the assay accurately identifies, for example, the 3.6% of patients with stage II who would benefit from treatment with adjuvant chemotherapy. If this analysis confirms that Previstage GCC helps improve outcomes and reduces the cost of care for patients with stage II colon cancer, coverage could become even more advantageous and widespread. Of course, the opposite could happen.

There is a current move away from traditional health maintenance organization plans (where these tests would be covered) toward more consumer-driven plans, preferred provider organization models, and some type of coinsurance. In these plans, members are going to have to pay at least part of the cost of these diagnostics. Depending on the economy and other factors, this trend could increasingly influence a patient's decision to choose chemotherapy and biomarker-based assays, such as Previstage GCC. The interest physicians and patients have in diagnostic guidelines and the effectiveness of the testing is illustrated by the recent events related to changes in mammogram and pap smear guidelines.

Several members of the study group suggested that Previstage GCC could follow the same reimbursement pathway as Onco*type* DX. One adviser pointed out that when Onco*type* DX first came to market, it was approximately 50% self-pay. Patients paid for it because they felt it was important. Over time, coverage for Onco*type* DX has grown, as has the overall value payers perceive in biomarker-based assays to help guide treatment decisions.

As the experience with Onco*type* DX illustrates, physician demand and patient support could affect the willingness of health plans to provide coverage and reimbursement for Previstage GCC.

Oncology guidelines, as well as the oncologists and societies that develop them (such as the National Comprehensive Cancer Network), can influence health plans' coverage policies for biomarker-based assays. These perceptions could reasonably be expected to mature as more data are gained regarding the potential value of biomarker-based assays in informed treatment decisions. Also, medical specialty associations are likely to require well-defined patient risk-stratification data to recommend the use of biomarker-based assays.

Data Needs of Managed Care

Health plans will review new biomarker-based assays to determine the appropriate approach to coverage and reimbursement. Almost all study group members suggested that when developing a coverage policy, health plans should require data that define the role an assay plays and the clinical and economic benefits it offers.

Manufacturers of biomarker-based assays can use several methodologies for developing the data that managed care requires. For example, payers can use retrospective analyses, registries, prospective trials, and pharmacoeconomic modeling to inform managed care's decision making. Such data also will enable medical specialty societies to develop treatment guidelines that incorporate the role of the assay and describe its impact on treatment decisions.

The data should determine why current treatment decisions are made and how the assay may help reduce the cost of care while maintaining or improving the quality of outcomes. For example, to support managed care's evaluation of Previstage GCC, a prospective registry study will collect information on why most patients with stage II colon cancer currently receive adjuvant chemotherapy. These data could determine whether Previstage GCC enables physicians to better decide who should and who should not be treated with adjuvant chemotherapy. As another example, studies should help determine whether Previstage GCC can help replace the histopathology portion of the process or other diagnostic tests (eg, CAT scans).

Several advisers suggest that bias could be an issue for any study involving a prospective registry. To minimize bias, a registry should include all patients with the disease addressed by the biomarker-based assays. Such a registry should be overseen by a qualified third party, such as a university or government agency.

Many health plans are open to providing retrospective data for evaluating the effectiveness of a diagnostic assay. The study group suggested that integrated delivery systems and group medical practices, such as the Department of Veterans Affairs, may be best positioned to provide the required data. The Pharmacy & Therapeutics Society has expressed interest in reaching out to such organizations to help advance the understanding of biomarker-based assays and their potential impact on treatment decisions, outcomes, cost, and the coverage review process.

Conclusions

Biomarker-based assays may enable providers to better determine the type of care that is appropriate for patients with colon cancer, especially patients with stage II. This provides an opportunity to improve outcomes and reduce the cost of care, which would be beneficial for payers and patients as well as providers. Achievement of this goal requires data that clearly define the biomarker-based assay's role in the delivery of care. Also required are additional data that risk-stratify the target patient populations and document the clinical and economic benefits afforded by the assay. Such data can be developed through a prospective registry, pharmacoeconomic models, and other approaches.

The role of biomarker-based assays is likely to become more important in the next few years. For example, payers are feeling increasing financial pressure from many directions. Healthcare reform and the potential for new government-sponsored plans and/or healthcare exchanges are one factor. The struggling economy limits the opportunity for health plans to pass along increased premiums to employers and employees. Many oncology drugs under development are likely to be much more costly than currently available chemotherapy. Medical advances in other disease states are increasing the competition for the limited healthcare funds available. In this environment, payers appreciate or even need the cost savings and improvement in outcomes that biomarker-based assays appear to be able to deliver.

Patients are increasingly sharing the cost of care through high-deductible plans and customer-driven health plans. Therefore, biomarker-based assays that deliver better outcomes and reduced cost of care offer potential value for patients and providers.

Although research is proceeding to determine whether the colon cancer results of Previstage GCC can be extended to rectal cancer staging, there currently are no firm conclusions. Data demonstrating Previstage GCC's usefulness for managing rectal cancer are likely to enhance the assay's value for managed care.

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Funding Source: Funding for this article was provided by DiagnoCure, Inc.

Author Disclosure: Dr Ross reports serving as a consultant/speaker or paid advisory board member for and receiving honoraria from DiagnoCure, Inc. Dr Jorgenson reports serving as a Pharmacy & Therapeutics Society board member. Dr Kaminsky reports serving as moderator for the study group from which this article was developed, and receiving payment for the development and preparation of this work.

The Pharmacy & Therapeutics Society (PTS) received funding from DiagnoCure, Inc., to convene the study group and develop this article. Four PTS board members served on the study group; one board member is a co-author.

Authorship Information: Concept and design (JJ, RK); acquisition of data (RK); analysis and interpretation of data (HR, JJ, RK); drafting of the manuscript (RK); critical revision of the manuscript for important intellectual content (HR, JJ, RK); obtaining funding (RK); and administrative, technical, or logistic support (RK).

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