SUPPLEMENT TO
MANAGED Care

The Impact of Molecular Diagnostics on Treatment Pathways, Outcomes, and Cost

Based on an educational symposium at the Academy of Managed Care Pharmacy 22nd Annual Meeting and Showcase, San Diego, April 6, 2010

HIGHLIGHTS

- Clinical Advances in Treatment Options and Diagnostics to Manage Breast Cancer and Colon Cancer
- Impact of Molecular Diagnostics on Health Outcomes and Cost
- Role of Molecular Diagnostics in Quality of Care Initiatives

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Introduction

MICHAEL J. FINE, MD
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Despite advances in treatment, cancer remains the second leading cause of death in the United States, surpassed only by cardiovascular disease. Lung, colorectal, and breast cancers are responsible for a large proportion of cancer-related deaths and remain difficult to treat. Second to lung cancer, breast cancer is the leading cause of cancer deaths in women (ACS 2010). The American Cancer Society estimates that in 2010, approximately 207,090 new cases of invasive breast cancer will occur among women and 1,970 among men, and an estimated 40,230 breast cancer deaths will occur among both women and men (ACS 2010). About 142,570 new cases of colorectal cancer, the third most common cancer in both men and women, are expected in 2010, with about 51,370 deaths, accounting for 9 percent of all cancer deaths (ACS 2010).

Data indicate that adjuvant chemotherapy can improve survival in patients with early-stage breast cancer or colorectal cancer who have undergone surgical resection, but the benefit from this treatment is not universal. Better methods are needed, therefore, to identify those patients whose disease is likely to recur and to avoid overtreating patients who are unlikely to derive a benefit.

In this continuing education publication, a distinguished panel of experts address the advances in molecular diagnostic testing and its impact on optimal care for patients with early-stage breast cancer or colon cancer. David M. Hyams, MD, FACS, discusses the epidemiology of breast and colorectal cancers, treatment options, and the new diagnostics that can be used to better manage patients. Cari Bruins, PharmD, discusses the impact of molecular diagnostics on health outcomes and cost in quality-of-care initiatives, and Winston Wong, PharmD, discusses the value of incorporating genomic testing into oncology treatment pathways.

Our intent in presenting these articles is to provide a better understanding of molecular diagnostic testing and to promote increased collaboration among all health care stakeholders to ensure optimal patient outcomes.

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ACS (American Cancer Society). Cancer Facts & Figures 2010. «http://www.cancer.org/Research/CancerFactsFigures/index». Accessed Sept. 10, 2010.

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A Continuing Education Activity

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Senior Medical Director, Health Net of California

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SELF-STUDY CONTINUING EDUCATION ACTIVITY

The Impact of Molecular Diagnostics on Treatment Pathways, Outcomes, and Cost

Needs Assessment

Health care costs are expected to double by 2017, reaching $4.3 trillion and consuming nearly one-fifth of the economy[1]. To halt the rising costs while increasing the quality of care and access to care, it is imperative to develop and disseminate information on effective medical interventions and the individualized treatments patients need. For example, most cancer drugs prescribed in the United States today are effective in fewer than 25 percent of treated patients[2]. When the first drug fails, a second or third drug is often prescribed.

Practice Gap

Oncologists currently use traditional factors to select adjuvant hormonal therapy and chemotherapy; however, new advances in genomics and molecular diagnostics provide a focus on the biology of a tumor to determine the aggressiveness and prognosis of the cancer and to predict the likely benefit from a specific treatment. These diagnostics can identify those patients that have a high risk of recurrence and, therefore, help reduce the risk of death as well as prevent the toxicity and expense of unnecessary treatment for low-risk patients. Physicians now have tools to individualize cancer treatment plans by guiding treatment decisions based on the genetic profile of an individual tumor. These predictive markers will indicate value for targeted biologic therapy and define choices of therapeutic strategies.

Description

This continuing education program provides information on the benefits of molecular diagnostics to determine appropriate treatment options for patients with breast cancer and colon cancer. The program analyzes the potential for cost savings and improved quality of life when using a strategy that has been identified as having a significant benefit to the patient. Managed care pharmacists will have the ability to assess the cost of treatment regimens as well as the cost of treating side effects and complications.

Learning Objectives

After reading this publication, participants will be able to:

- Review the epidemiology of breast and colon cancer as well as clinical advances in treatment options and diagnostic testing for optimal care.
- Determine the economic impact of molecular diagnostics in the identification of early-stage breast and colon cancer, allowing individualized treatment options.
- Assess best practices in health plan oncology management programs utilizing molecular diagnostics with respect to individualizing treatment decisions, outcomes, quality of care, and cost.

[1] Keenan S, Sisko A, Truffer C, et al. Health spending projections through 2017: the baby-boom generation is coming to Medicare. *Health Aff*. 2008;27:145–155.

[2] Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. *Trends Mol Med*. 2001;7:201–204.

Target Audience

This program is intended for the education of managed care medical directors, pharmacy directors, clinical pharmacists, and other healthcare decision makers in managed care organizations, health systems, academia, and industry.

Method of instruction

Participants should read the learning objectives and the articles in this supplement and review the activity in its entirety. Participants should then complete the post-test and submit the assessment/evaluation form with the text answers. Upon achieving a passing score of 70 percent or better on the post-test, a statement of credit will be awarded.

Accreditation

CE Credit for Pharmacists

The Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education accredits the University of Arizona College of Pharmacy.

This program is approved for 1.5 contact hours (0.15 CEU). ACPE Program Number 0003-999910-020-H01-P.

CE Credit for Physicians

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME). The University of Arizona College of Medicine at the Arizona Health Sciences Center is accredited by the ACCME to provide continuing medical education for physicians.

The University of Arizona College of Medicine at the Arizona Health Sciences Center designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Conflict-of-interest policy and disclosures of significant relationships

As a sponsor accredited by the ACCME, the University of Arizona College of Medicine at the Arizona Health Sciences Center must ensure balance, independence, objectivity, and scientific rigor in all its sponsored educational activities. Faculty members must disclose to the activity audience any significant financial interest or other relationships that may affect their presentation. The faculty has disclosed the following:

Cari Bruins, PharmD, Michael J. Fine, MD, and Winston Wong, PharmD, have no real or apparent conflicts of interest to report. David M. Hyams, MD, has received grant/research support from AstraZeneca and Centocor Ortho-Biotech. He is a consultant for Genomic Health and Aptium Oncology and is on the speakers' bureau of Genomic Health.

The University of Arizona College of Pharmacy and Medicine at the Arizona Health Sciences Center Continuing Medical Education Committee Disclosures 2009-2010:

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Clinical Advances in Treatment Options and Diagnostics: New Tools in the Management of Breast Cancer and Colon Cancer

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EPIDEMIOLOGY

Excluding nonmelanoma skin cancers and *in situ* carcinomas, breast, lung, and colorectal cancers in both men and women represent the largest number of incident cancers in the United States. More than 190,000 new cases of invasive breast cancer and 150,000 colorectal cancers are diagnosed every year (ACS 2010). Although the incidence and mortality of invasive breast cancer has steadily risen over the last 50 years, that trend has recently begun to reverse (ACS 2010). Since 1990, there has been a marked decrease in breast cancer mortality in most industrialized countries (Autier 2010). Some of that decline may be attributed to earlier detection as well as improvements in both local and regional therapy, but most of the decrease is likely due to the widespread adoption of effective systemic treatments.

BREAST CANCER DIAGNOSIS AND TREATMENT

In May 1988, the National Cancer Institute (NCI) issued a clinical alert signaling an important change in the management of early-stage breast cancer (Johnson 1994). That alert encouraged the consideration of systemic intervention by stating that adjuvant hormonal or cytotoxic therapy could have a meaningful impact on the natural history of node-negative breast cancer patients (Johnson 1994). Until that time, adjuvant treatment with chemotherapy had been largely reserved for patients with higher-risk node-positive disease, despite the significant risk of relapse among patients with hormone-responsive node-negative tumors. The alert also recognized the results of large prospective clinical trials that had good safety profiles and produced meaningful reductions in risk of recurrence. By 2000, adjuvant chemotherapy for women with node-negative hormone receptor-positive breast cancer became a standard of care.

Further support for cytotoxic chemotherapy in early-stage breast cancer came from a large-scale meta-analysis (EBCTCG 2000). In reviewing the major prospective randomized clinical trials in which polychemotherapy was compared with no treatment, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated a consistent 23 percent reduction in disease recurrence associated with chemotherapy. This analysis included data from 56 clinical trials representing more than 28,000 women with a minimum of 5 years follow-up. Although the data confirmed the value of adjuvant polychemotherapy, the data also suggested that more than 40 percent of the women entering these trials would never have disease recurrence — they had already been cured by surgical intervention. Unfortunately, a similar proportion of women, destined to relapse, did so despite receiving protocol-directed polychemotherapy (EBCTCG 2000). For these women, chemotherapy was ineffective against the unique biology of their particular tumor.

These data illustrate the challenge still faced in modern oncology management — how to identify those patients who are likely to be cured by surgery alone, thereby avoiding additional unnecessary treatment, while also identifying those patients likely to have disease recurrence and choosing the most effective treatment for each of them. Recent efforts suggest that future success will come from a better understanding of a tumor's intrinsic biology that influences both risk of relapse and therapeutic response. The impact would be greatest if applied to the most prevalent tumors such as breast and colorectal cancers.

Use of molecular taxonomy in prognosis of breast cancer

Sophisticated DNA analysis and gene-expression profiling provide a window into tumor cell biology and may be used to better classify tumors than traditional micro-

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scopic evaluation. An early study by Perou (2000) examined and grouped similar gene-expression patterns of breast cancer, suggesting five molecular subtypes: Luminal A, luminal B, basal-like, normal-like, and human epidermal growth factor receptor 2 (HER2) positive. "Luminal" and "basal-like" refer to expression patterns of the relevant normal cytokeratins. Subsequent research has confirmed notable differences in clinical behavior between these subtypes, classified by gene expression patterns. Patients in the hormone-receptor-positive luminal A group tend to have a much better prognosis than the similarly hormone-receptor-positive luminal B group. Both of these have lower early-disease recurrence rates than those with tumors of the basal-like subtype (largely clinically triple-negative), or the HER2 subtype (principally HER2 overexpressing).

Perou's approach (2000) to classification is based upon an *unsupervised* analysis of gene expression. In an unsupervised analysis, tumor subtypes are simply collections of individual tumors grouped by similar patterns of gene over- or under-expression. An alternative approach to gene expression evaluation is *supervised* analysis. With this approach, a discriminator is selected and genes are chosen that appear to consistently correlate their over- or under-expression with the particular analytic discriminator. A commonly chosen discriminator of clinical relevance has been distant relapse. Genes may be evaluated from a large "global" gene set using microarrays of tens of thousands of expressed sequence tags, or may be analyzed from a smaller selected set of likely relevant genes using quantitative reverse transcriptase polymerase chain reaction (RT-PCR). Perou's unsupervised classification approach has been refined into a more practical and clinically oriented assay distilled down to 50 genes. This PAM50 assay is currently in commercial development. Several assays have been derived from the supervised approach, some of which have already been commercialized and some of which are currently in commercial development.

PAM50 assay. PAM50 is a gene expression assay developed from Perou's (2000) original subtypes. A total of 189 breast cancers across 1,906 intrinsic genes were evaluated by hierarchical analysis in order to construct idealized prototypes for each of four main classifications. Normal-likes were excluded as they seemed more representative of normal tissue contamination rather than a distinct tumor subtype. Sophisticated statistical tools were used to create a reduced gene set derived from the prototype samples, which was accomplished using gene expression data from quantitative RT-PCR. By utilizing an appropriate scoring algorithm, the assay was designed to provide a continuous risk of recurrence score based on the similarity of an individual specimen to each of the prototypic subtypes.

Parker (2009) studied the utility of the PAM50 assay, which described intrinsic subtypes luminal A, luminal B, basal-like, and HER2-enriched for predicting the risk of relapse in a cohort of untreated breast cancer patients. Interestingly, although the expected phenotypic subtypes (ER+, triple-negative, and HER2-positive) were predominantly represented in the expected genotypic subtypes, each subtype included some tumors that were clinically ER-positive, ER-negative, HER2-positive, and HER2-negative, suggesting that a traditional clinical assessment is not sufficient to provide accurate biologic classification consistent with the gene expression subtypes. The intrinsic subtypes defined by the PAM50 assay demonstrated overall prognostic significance for the evaluated patients. PAM50 was a strong predictor of outcome in multivariate analyses that incorporated standard clinical parameters, including ER status, histologic grade, tumor size, and nodal status. The prognostic utility of this assay in untreated patients is shown in Figure 1 with each subtype broken into clinically relevant groups based on ER and HER2 expression. A second group of patients whose tumors were subjected to PAM50 analysis had received neoadjuvant chemotherapy, which included paclitaxel, fluorouracil, doxorubicin, and cyclophosphamide. The assay predicted the efficacy of neoadjuvant chemotherapy with a negative predictive value for complete pathologic response (pCR) of 97 percent.

Thus far, attempts to replicate PAM50 in other centers have produced inconsistent results, raising questions as to the reproducibility of the assay. Parker and Perou (Perou 2010) have suggested that discrepancies among different laboratories reflect poor internal controls and a lack of testing standardization. These issues remain to be addressed as PAM50 continues toward commercialization.

MammaPrint (Amsterdam 70-gene assay/Agendia). The MammaPrint assay was developed using a DNA microarray analysis of tissue samples from 61 patients maintained in a frozen tissue archive at the Netherlands Cancer Institute. The analysis identified a 70-gene set that correlated with an individual patient's outcome. Also known as the Amsterdam 70-gene profile, the assay evaluated 295 frozen tissue specimens of patients with node-negative and node-positive breast cancer who were 53 years old or younger at the time of diagnosis and whose tumors were less than 5 cm in size (van de Vijver 2002). The patient group included both hormone-responsive and hormone-unresponsive breast cancers.

In the initial study, van de Vijver (2002) chose to use an algorithmic approach that separated patients into good-prognosis signature and poor-prognosis signature categories, and this designation has persisted in the commercial assay. The study showed a 10-year survival rate of 55 percent for patients with a poor-prognosis signature and a 10-year survival of nearly 95 percent for patients with a good-prognosis signature. The probability

of remaining free of distant metastases was approximately 50 percent and 85 percent, respectively. In comparing the two signature categories, a hazard ratio (HR) of 5.1 (95% CI, 2.9-9.0; *P*<.001) was identified. Of particular interest was the fact that nearly 40 percent of the younger patients had a 10-year risk of distant disease recurrence that was less than 10 percent. Based on the constant expected proportional risk reduction from chemotherapy, the clinical benefit for low-risk patients receiving chemotherapy would be minimal.

The initial Amsterdam study was criticized for including the same 61 patients used to develop the assay in the final validation study of 295 patients. The authors stated that they included the original test set of patients, because they were originally selected based on a disproportionately high rate of recurrence. There was concern that exclusion from the validation set would have left too few recurrences for analysis and might have introduced selection bias.

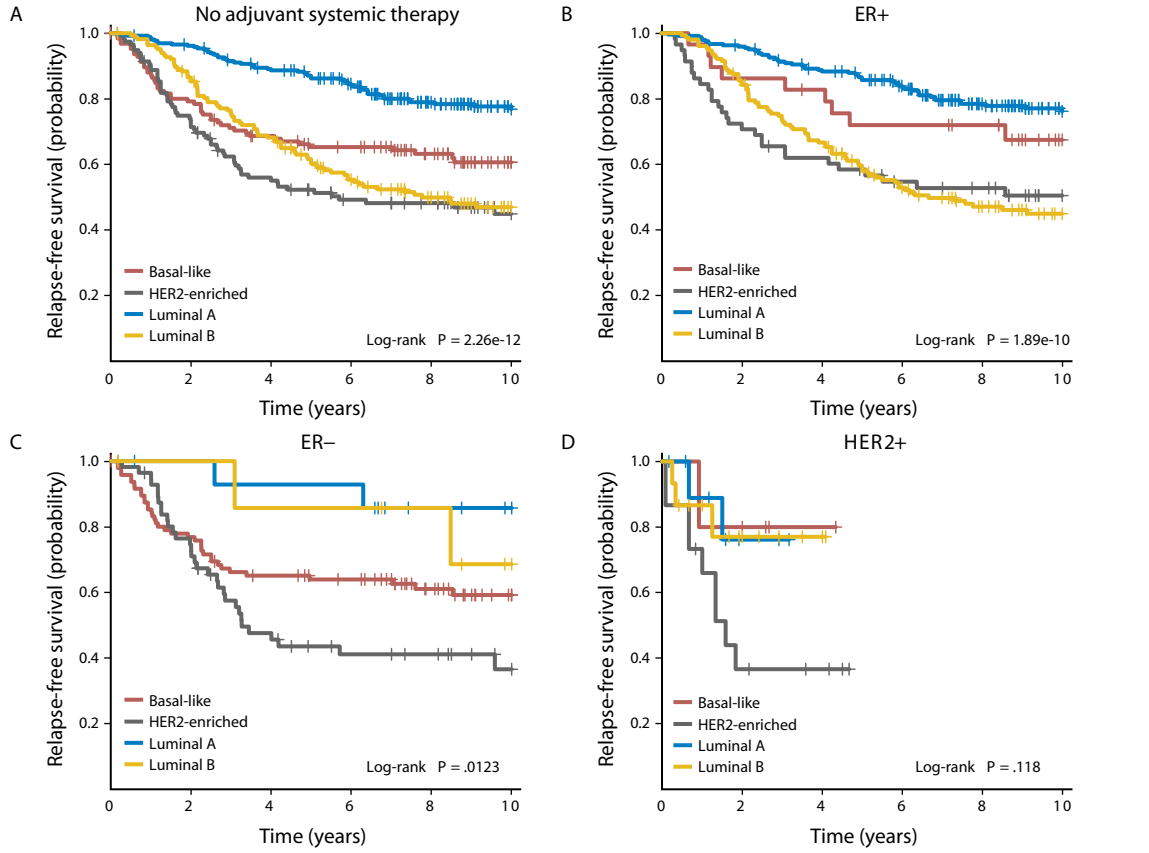
To confirm the value of the 70-gene assay, the TransBIG validation trial (Piccart-Gebhart 2004), conducted with the Breast International Group, utilized 307 patients with 137 recurrence events in whom frozen tissue was available as well as long-term follow-up (median greater than 13 years). Patients were sorted into low-risk and high-risk groups with low risk again having a distant recurrence risk of less than 10 percent at 10 years. The clinical risk assessment tool *Adjuvant! Online* was used to sort the same patients into low- and high-risk groups with similar cutoffs. The study showed that the 70-gene assay more accurately assigned risk, outperforming the assessment tool with an HR of 2.32 (95% CI, 1.25-4.0).

The TransBIG study suggested that many breast cancer patients might be inaccurately risk classified when

FIGURE 1

PAM50 assay – intrinsic subtype prognosis for relapse-free survival

A. Outcome predictions according to the four tumor subtypes in a test set of 710 node-negative, no systemic adjuvant therapy patients. **B**. Outcome by subtype in the subset of patients with estrogen-receptor (ER)-positive disease* from 1A. **C**. Outcome by subtype in patients with ER-negative disease.* **D.** Outcome by subtype in HER2-positive patients.*



*Clinically determined.

Source: Parker 2009

only clinical and pathologic criteria are used for assessment. In TransBIG, 33 percent of a cohort that would have been classified as low risk by traditional methods turned out to be high risk when assessed by molecular expression. These patients might well have been undertreated if chemotherapy were not offered. Conversely, 36 percent of a group of patients that would traditionally have been considered at high risk turned out to be low risk and, therefore, would have derived little practical benefit from a prescribed cytotoxic adjuvant therapy based only on clinicopathologic assessment.

MammaPrint has been commercialized and is available in both Europe and the United States and its use is recommended by the St. Gallen European Conference for Cancer Treatment guidelines. However, MammaPrint must be ordered before the tumor is resected; the test requires special preservation techniques for storing the tissue, which must be accomplished before formalin fixation. As in the original test, tissue may be either flash frozen or stored in RNA-friendly preservative at the time of surgery. As a result, Agendia has offered cost-free acquisition and storage until a clinician decides whether to utilize the assay. The inability to use historical tissue limits retrospective analyses of clinical trial samples where the tissues have been RNA preserved. As a result, MammaPrint has not yet been able to demonstrate the kind of therapy-related predictive value for its assay that comes from the direct evaluation of well-defined patient groups prospectively randomized to differing treatment strategies. Knauer (2010) has published data demonstrating a correlation between patients classified as high risk by MammaPrint and response to neoadjuvant chemotherapy; however, there are no data that confirm MammaPrint's value in predicting improvement in long-term distant disease-free survival (DDFS).

In Straver's neoadjuvant study (2010) at the Netherlands Cancer Institute, 167 consecutive patients who received neoadjuvant chemotherapy for Stage II or III breast cancer had pretreatment specimens subjected to the MammaPrint assay. Of the 144 patients who were classified as high risk, 20 percent had a pCR, whereas none in the low-risk group achieved pCR. These data suggest that the MammaPrint low-risk patients do not have tumor biologies that are susceptible to cytotoxic chemotherapy. However, there is little to suggest an improvement in drug selection for the higher-risk patients whose pCR differed little from the unselected patients receiving neoadjuvant chemotherapy consisting of doxorubicin+cyclophosphamide (AC) in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial (13 percent) or AC + docetaxel in the NSABP B-27 trial (26 percent) (Bear 2006, Wolmark 2001). Knauer (2010) has demonstrated an improved 5-year breast cancer specific survival (BCSS) among a MammaPrint high-risk group from a pooled study series of 541 patients who received either postoperative endocrine therapy alone or endocrine therapy plus chemotherapy. Although patients in the low-risk group, representing 47 percent of the study population, received no apparent benefit in BCSS, the benefit of the addition of chemotherapy to the high-risk group translated to an increase in BCSS from 81 percent to 94 percent (HR=0.21, 95% CI, 0.07–0.59; $P<0.01$).

Onco*type* DX (21-gene assay/Genomic Health). The Onco*type* DX assay is a multigene test that predicts outcomes for patients with ER-positive, lymph-node–negative breast cancer. The assay uses quantitative RT-PCR technology that is more forgiving of formalin preservation and long-term storage in paraffin and was specifically constructed to make use of such archival tissue, allowing the developers to utilize previously conducted prospective randomized trial data sets and tissue archives for both assay development and validation (Cronin 2004). Using tissue from two large hospitals and from the tamoxifen-only treatment arm of the NSABP B-14 trial, a 21-gene panel was developed comprised of 16 cancer outcome genes and 5 "housekeeping" genes used for cross assay normalization (Paik 2004a). An algorithm also was designed that factored in the expression of these genes and the relative importance of their over or underexpression. From this algorithm, a numerical "recurrence score" was computed for each tumor sample (Paik 2004a). The recurrence score can range from 0 to 100 and can be plotted against a 10-year risk of recurrence. This approach allows an individualized assessment of prognosis potentially more informative than a simple binary good or poor risk.

Although the Onco*type* DX assay was designed to provide an individual recurrence score, patients can be grouped into risk categories for comparative purposes and statistical analysis. For any assay that calculates individual risk, such groupings are inherently arbitrary; the division may be binary, or patients may be separated into tertiles, quartiles, etc. With Onco*type* DX, three groupings were chosen — low, intermediate, and high — to provide adequate sample size and to identify a low-risk group not likely to have clinically significant benefit from the modest outcome improvement of cytotoxic therapy. Similar to MammaPrint, the Onco*type* DX low-risk category was designed to include only those patients with an overall risk of distant recurrence of less than 10 percent at 10 years.

Validation of the assay was based on a retrospective analysis of 668 tumor samples obtained from tamoxifen treated patients with node-negative, ER-positive tumors enrolled in NSABP B-14 (Paik 2004a). Results showed that the difference in risk of distant recurrence between patients with low recurrence scores and those with high recurrence scores was large and statistically significant. More than half of the patients in the study were catego-

rized as low risk with a mean rate of distant recurrence of 6.8 percent at 10 years. Just over one quarter of the validation set's patients (27 percent) were categorized as high risk with a mean risk of 30.5 percent for distant recurrence at 10 years. Paik (2004b) also demonstrated that the 21-gene recurrence score could be used to more effectively classify patients than traditional clinicopathologic approaches. In a separate study (Paik 2004c), the 668 patients in the Onco*type* DX validation set were placed into either a low-risk category or a high-risk category using NCCN or St. Gallen criteria that relied on clinicopathologic factors such as age, tumor size, and tumor grade. Although these low-risk patients had a 10-year distant recurrence risk of 7 percent and 5 percent, respectively, only 7.9 percent of the 668 patients could be classified as low risk by clinicopathologic criteria. However, using Onco*type* DX, more than 50 percent was classified as low-risk with a similar 10-year distant recurrence-free survival (DRFS) of 93 percent (Table).

TABLE
Onco*type* DX validation set – Kaplan-Meier estimate of 10-year distant recurrence-free survival (DRFS)

	NCCN Criteria		St. Gallen Criteria		Recurrence Score	
Risk category	**% of patients**	**10-year DRFS**	**% of patients**	**10-year DRFS**	**% of patients**	**10-year DRFS**
Low	7.9	93%	7.9	95%	50.6	93%
Intermediate	—	—	33.2	91%	22.3	86%
High	92.1	85%	58.8	81%	27.1	69%

NCCN=National Comprehensive Cancer Network
Source: Paik 2004c

Whereas Onco*type* DX demonstrated prognostic value in the NSABP B-14 validation trial, paraffin-embedded samples from both the NSABP B-14 and B-20 trials provided a unique opportunity to evaluate predictive efficacy of the assay for two randomized treatment groups. In B-14, patients were randomized either to no treatment or to tamoxifen, whereas in B-20, patients were randomized to receive either tamoxifen alone versus tamoxifen with cyclophosphamide+ methotrexate+ fluorouracil (CMF) or tamoxifen with methotrexate followed by fluorouracil chemotherapy (M->F). Outcomes for both chemotherapy arms in the B-20 trial were sufficiently similar that, for the purpose of this discussion, CMF and M->F are considered "chemotherapy."

In the NSABP B-14 trial, 645 of the 2,817 randomized patients had paraffin-embedded samples available for analysis. Among these patients, the proportional tamoxifen treatment benefit was consistent with that of the original B-14 study. Closer inspection, however, would suggest that the greatest treatment benefit of tamoxifen was concentrated in the low- and intermediate-risk patients. Since the *P* value for global interaction between recurrence score group and tamoxifen benefit did not reach statistical significance ($P=.06$), the data continue to support the consideration of anti-estrogen therapy in all node-negative, ER-positive patients. However, the treatment group trends suggest that the greatest benefit is likely to be in patients with a low or intermediate risk of recurrence. In NSABP B-20, there were 651 patient samples available out of the 2,363 women entered in the original trial. This subset had a similar chemotherapy-associated DDFS improvement (4.4 percent) as did the originally randomized B-20 cohort. In this analysis, there was a statistically significant interaction between recurrence score and chemotherapy benefit ($P=.038$). Further examination of these results suggests that the benefit of chemotherapy was largely confined to patients with high recurrence scores. Unlike the 23 percent risk reduction for polychemotherapy reported by the EBCTCG (2000), this group of patients had a 75 percent risk reduction from the chemotherapy to tamoxifen, and drove the benefit seen in the overall trial (Paik 2006).

These data have led to recommendations by the American Society of Clinical Oncology and the National Comprehensive Cancer Network (NCCN 2010a) that the 21-gene Oncotype DX assay be considered in patients with ER-positive, node-negative disease. Many institutions have adopted this approach to treatment. Liang (2007) conducted a study at the University of Pittsburgh Hillman Cancer Center that showed the results of the Onco*type* DX assay significantly reduced the number of patients for whom adjuvant chemotherapy was recommended. As a result, nearly all (95 percent) of low-risk patients were recommended to receive only hormonal therapy. Conversely, the vast majority of high-risk patients did receive both hormonal and adjuvant chemotherapy. Given the uncertainty of benefit to "average risk" patients in the intermediate risk group, it is not surprising that the authors reported equipoise, with approximately half of patients receiving adjuvant chemotherapy. The results of prospective randomized trials, such as the recently closed Trial Assigning Individualized Options for Treatment (Rx) (TAILORx), which began May 2006, should provide a better means to evaluate patients at intermediate risk (NCI 2010a).

Nodal status in breast cancer prognosis

In multivariate analyses, nodal status consistently appears as the most important predictor of distant breast cancer recurrence. Numerous clinical trials have demonstrated the value of polychemotherapy in the setting of node-positive disease. As a result, node-positive regimens have incorporated additional potent, if somewhat toxic, agents and take advantage of growth factor support to intensify treatment. Because of the adverse impact of lymph node involvement, polychemotherapy has become a standard consideration for all but the most elderly or frail node-positive patients.

The relationship between recurrence score and response of node-negative patients to chemotherapy suggests that not all breast cancers are biologically responsive to polychemotherapy. Data from the Eastern Cooperative Oncology Group (ECOG) study E-2197 (Badve 2008) shows that node-positive as well as node-negative breast cancer patients treated with polychemotherapy and tamoxifen can be divided into statistically meaningful groups of lower risk, higher risk, and intermediate risk using the Onco*type* DX assay. Similarly, 8814 node-positive, tamoxifen-treated patients in the Southwest Oncology Group (SWOG) study (Albain 2010) with suitable archival tissue available could be separated into the same three risk groups after individual Onco*type* DX risk assessment. In this exclusively node-positive population, even the lowest-risk group, comprising 40 percent of the tested population, had a 10-year disease-free survival (DFS) of only 60 percent. The SWOG 8814 did demonstrate overall improvement in both DFS and overall survival (OS) when comparing tamoxifen alone with a "modern" regimen of AC and fluorouracil (CAF) followed by sequential tamoxifen. However, when the efficacy of therapy was evaluated in the 347 patients in whom suitable tissue was available, it became evident that the lower-risk group derived no apparent benefit from CAF therapy. In fact, that group had a numerically inferior outcome. As in the B-20 analysis, the overall benefit seen from the addition of cytotoxic chemotherapy came from the 32 percent of patients with high-risk recurrence scores. These data suggest the need for prospective studies evaluating alternative treatment strategies in these lower-risk node-positive patients.

COLON CANCER DIAGNOSIS and TREATMENT

As in breast cancer, a reliable recurrence score for patients with colon cancer could be useful in clinical decision making. Prognosis and treatment of colon cancer has been largely based on disease stage. Studies have shown unequivocal benefit to adjuvant chemotherapy in patients with Stage III disease (Sargent 2008). The value of such therapy in Stage II disease has long been debated however. Although the Surveillance, Epidemiology, and End Results (SEER) database for 1991–2000 (NCI 2010b), with 119,363 colon cancer patients, showed a 5-year mortality for all Stage II patients of 17.5 percent, it was only 15.3 percent for those with Stage IIa (T3N0) colon cancer, but 27.8 percent for Stage IIb (T4N0). Approximately 15 percent of Stage II patients have Stage IIb disease. The magnitude of their risk is such that this group would be expected to derive benefit from even the moderate proportional risk reduction possible with current chemotherapy regimens. It remains unclear, however, which patients with Stage IIa disease have sufficient risk for such treatment.

Surgery alone will be curative in many patients with Stage IIa disease. Furthermore, today's standard fluorouracil-based (FU) chemotherapy regimens appear to result in significant, but limited, proportional benefit. Short- and long-term toxicities can be particularly troublesome, especially in older patients. Thus, the selection of candidates for chemotherapy is often highly subjective and is commonly based on age, presence of comorbidities, and the patient's individual preference as much as on standardized risk assessment using a limited set of clinical and pathologic markers. Given a median age of 71 and the associated comorbidities of this patient population, it is not surprising that only a minority are referred for medical oncology evaluation. As a result many individuals who might benefit from modern therapy remain untreated.

Microsatellite instability. Ongoing research has increased knowledge about colorectal cancer on a molecular level and has provided an important tool for the assessment of early-stage colon cancer.

During normal eukaryotic division, it is not uncommon for errors in DNA replication to occur, which may affect the long stretches of DNA that exist between coding genes, known as microsatellites. Because of long, repetitive nucleotide sequences, a "mismatch" can occur between strands leading to small "loops" of DNA that mismatch out of proper sequence. When this occurs, it is addressed by a mismatch repair (MMR) protein complex consisting of 4 subunits. When there are germline or acquired abnormalities in the components of the MMR complex, the DNA mismatch abnormalities are not repaired, giving rise to microsatellite instability (MSI). The occurrence of MSI facilitates the development of colon cancer (Imai 2000, Umetani 2000).

Microsatellite instability has been detected in 10 to 20 percent of all spontaneous colorectal cancers and in nearly all colorectal carcinomas associated with hereditary nonpolyposis colorectal cancer or Lynch syndrome (Imai 2008, Umetani 2000). In fact, this DNA mismatch is a hallmark of tumors associated with Lynch, making MSI a useful screening marker for patients with this syndrome (Imai 2008). Perhaps surprisingly, patients with tumors exhibiting high-frequency MSI have better outcomes when compared with stage-matched patients

without this feature (Ribic 2003). In sporadic colorectal cancer, high-frequency MSI occurs more frequently in tumors located proximal to the splenic flexure. Although these tumors tend to be large, they often have a more favorable stage distribution. While high-frequency MSI confers a particularly favorable prognosis, MSI-associated tumors appear to be less responsive to FU-based therapy and have a poorer outcome (Ribic 2003). These findings have been confirmed and extended recently by Sargent (2010). The investigators concluded that the stratification of patients according to MMR status could provide a more individualized approach to the use of adjuvant chemotherapy.

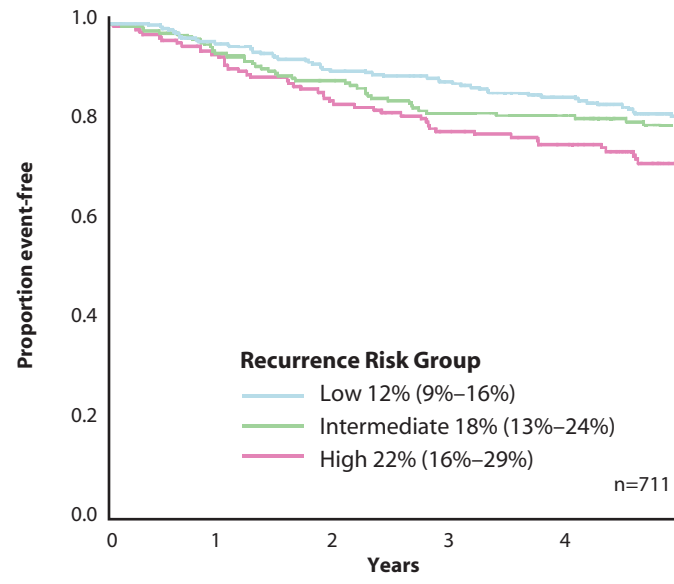
Oncotype DX colon cancer assay/Genomic Health

Excluding patients with high-risk T4 disease and those with lower-risk MMR-deficient disease, leaves 70 percent of patients with Stage IIa disease for whom there is no validated guidance for selecting adjuvant chemotherapy. For these patients, more suitable predictors of prognosis and response to treatment are required. To address this need, Genomic Health developed an assay using an approach very similar to that used for its breast cancer Oncotype DX assay. Candidate genes for the assay were drawn from four studies (Kerr 2009, Lavery 2008; O'Connell 2006, 2008) conducted by the NSABBP and from patient material at the Cleveland Clinic. A total of 761 genes from 1,851 patients were evaluated. When analyzed against outcome and response to therapy, genes were selected and a scoring algorithm developed for two assay components. One of these was designed to assess risk of disease recurrence and prognosis (7 genes), while another was developed to predict response to 5FU-based therapeutic regimens (6 genes). As with the breast assay, housekeeping genes were selected for cross-assay standardization (5 genes).

To validate the selected assay, a large number of patient blocks were required from a study (Quasar 2007) that compared no adjuvant treatment with modern FU-based adjuvant chemotherapy. The QUick And Simple And Reliable (QUASAR) clinical trial was particularly well suited to serve as the necessary validation study. QUASAR had demonstrated improved survival of patients with Stage II colon cancer with adjuvant chemotherapy with 5FU and folinic acid. The relative risk of death from any cause among patients who received adjuvant chemotherapy compared with a no-treatment control group was 0.82 (P=.008), while the relative risk of recurrence with chemotherapy versus observation alone was 0.78 (P=.001). Assuming an overall 5-year mortality rate without chemotherapy at 20 percent, QUASAR suggested that this regimen would result in a 3 percent to 4 percent absolute improvement in survival (QUASAR 2007).

Tumor specimens were available for 68 percent of Stage II colon cancer patients who participated in QUASAR, with a final evaluable population of 1,436 (711 who underwent surgery alone and 725 with surgery plus FU and leucovorin (5FU/LV). In a primary analysis of these patients, the recurrence score predicted the risk of disease recurrence at 3 years (P=.004), DFS (P=.01), and OS (P=.04). The risk of disease recurrence increased monotonically with an increasing recurrence score. In multivariate analyses, the algorithm remained prognostic (P=.008) independent of MMR, tumor stage, nodes examined, grade, and lymphovascular invasion. However, the study did not meet its secondary goal of validating a separate predictive treatment score that would predict re-

FIGURE 2
QUASAR Study Results – Population distribution and recurrence risk by recurrence score (RS)



Recurrence Risk Group	Range of RS	Proportion of patients
Low	<30	43.7%
Intermediate	30–40	30.7%
High	≥41	25.6%

Source: Kerr 2009

sponse to 5FU/LV adjuvant therapy (Kerr 2009).

As in the breast assay, patients were separated into high-, intermediate-, and low-risk groups for analytical purposes and treatment consideration. Based on the recurrence score, nearly 44 percent of patients in the study fell into a low-risk group with a 3-year DRFS of 12 percent (95% CI, 9%-16%) (Figure 2). These patients would gain an expected absolute treatment benefit of 5FU/LV of 2.4 percent, providing little incentive for therapy. Conversely, one-quarter of patients were deemed high-risk, with a 3-year distant disease recurrence risk of 22 percent (95% CI, 16%-29%). These individuals would have the same proportional benefit of 5FU/LV chemotherapy but would get an absolute improvement in distant DFS of 4.4 percent. This is consistent with the absolute improvement seen with the addition of Oxaliplatin in patients with Stage III disease.

Although the Onco*type*DX assay for colon cancer cannot predict response to chemotherapy, it can identify those patients with a higher risk for relapse who might derive more absolute benefit from chemotherapy. It also may provide a useful addition to the clinical information that is already used.

ColoPrint colon cancer assay/Agendia

Assays using genome-wide c-DNA microarray supervised analysis are also in development. Most notable is Agendia's ColoPrint assay. Using archived frozen tissue from 138 Stages I, II, and III colorectal cancer patients, a 38-gene prognostic "signature" was developed using techniques similar to those used for the MammaPrint breast assay (Salazar 2010a). Validation of the gene panel was conducted in an independent cohort of 18 patient samples and in 322 patients from *in-silico* data sets (Salazar 2010a). The gene expression signature was then evaluated against standard clinicopathologic predictors of outcome. As with MammaPrint, ColoPrint utilizes a binary classification, and 61 percent of patients were classified as low risk and 39 percent as high risk. There was a significant difference in distant metastasis free survival (DMFS) between the low-risk and high-risk groups, with an HR of 3.2 (P=.0008). The 5-year DMFS rate was 89 percent (95% CI, 83%-95%) for low-risk patients and 62 percent (95% CI, 50%-77%) for high-risk patients. In a multivariate analysis, ColoPrint remained the most prognostic factor with an HR of 2.95 (P=.015). ColoPrint showed significant performance in Stages II (P=.0058) and III (P=.036) patients. Patients with MSI were mainly low risk (86 percent) (Salazar 2010a). The assay is now on an Agilent platform to allow high-throughput commercialization. An additional prospective validation trial is in progress. The Prospective Analysis of Risk Stratification by coloPrint (PARSC) study (Salazar 2010b) is a multinational, prospective observational study that will compare the ColoPrint risk assessment outcome with local and nationally accepted clinicopathological predictors of outcome. It is expected to accrue 700 patients. Commercialization of this assay is expected in 2010.

Practical Management

The most useful approach to assessing patients with early-stage colon cancer might be to combine T-stage, MSI/MMR status and a well-validated gene expression assay. QUASAR analysis shows each to be an independent predictor of outcome. The T4 group has the highest base risk and will get the largest absolute outcome improvement from the constant proportional benefit of adjuvant chemotherapy. The MMR-deficient group is likely to have the best prognosis and thus the lowest absolute benefit from adjuvant chemotherapy. New molecular diagnostics, such as the commercially available Onco*type* DX, might then focus on the less certain middle group. If those in the non-MMR deficient and non-T4 population can be shown to have a risk at least as great as the T4 population, then they too might consider chemotherapy. The remainder would be well served by a test that helps them to avoid treatment likely to offer little practical benefit. It is clear that continued efforts are urgently needed to identify gene panels that are more predictive of response to specific therapies. Such panels will go a long way to improving the rational choice of treatment for patients with early-stage colon cancer.

CONCLUSION

High-throughput gene-expression technologies provide a rapid and reliable means to interrogate common early-stage cancers about their biological risk. Their utility can assist physicians and patients to make critical treatment decisions among a variety of adjuvant treatment strategies. In some cases, these assays may be more than prognostic, with an ability to predict response to different types of therapy. Yet, these tests are only the first step in moving to a more personalized approach to cancer treatment. Increasingly important will be the development of assays that predict response to specific agents already in the anticancer armamentarium and assays that identify key controller genes against which future therapeutic agents will be developed.

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Implications of Molecular Diagnostics on Health Outcomes and Cost in Quality-of-Care Initiatives

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EVALUATING GENETIC AND DIAGNOSTIC TESTS

A health technology assessment can be defined as the unbiased evidence-based review of the safety and efficacy of a new or emerging — and sometimes controversial — health care technology. Recent breakthroughs in biologics, antivirals, diagnostic imaging, molecular diagnostics, organ and tissue replacement, and surgical techniques have helped to greatly improve health care delivery and patient outcomes. A technology assessment offers a bridge between research in these breakthroughs on one end and real-world applicability on the other end.

Technology assessments address the opportunities and challenges of genetic and pharmacogenomic testing. Molecular diagnostics are personalized medicine technologies that present opportunities to improve patient outcomes. Medical treatment can be tailored to individual patients to improve patient care and at the same time reduce the costs associated with that care. Personalized medicine has the potential to improve healthcare through earlier diagnosis and, therefore, more effective treatment by guiding the selection of drug therapies to improve efficacy and avoid toxicity.

A number of challenges surround the evaluation and use of genetic and diagnostic technologies. First, there is weak regulatory oversight. Federal regulation of genetic and diagnostic tests comes under the auspices of two agencies: The U.S. Food and Drug Administration and The Centers for Medicare and Medicaid Services. The FDA only monitors tests that are sold directly to laboratories; however, most genetic/diagnostic tests are laboratory-developed tests (LDTs) that are not reviewed by the FDA, and FDA approval is not necessary for laboratories to bring their tests to market. The Clinical Laboratory Improvement Amendments of 1988 (CLIA), which is overseen by CMS, regulate the laboratories that develop LDTs. The quality of laboratory testing can be an issue, as it can vary considerably. Currently, CLIA does not specify particular laboratory protocols, and most genetic/diagnostic testing laboratories are not required to perform proficiency testing.

Another challenge is that there are no evidence-based standards for clinically validating either genetic or molecular diagnostic technologies. Clinical utility — the demonstration that test results can change patient management decisions and improve net health outcomes — is important to establish in order to translate test results into clinical practice. The number and quality of studies establishing clinical utility are limited; therefore, the interventions and outcomes based on test results often are not well defined. According to an April 2008 Report of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), U.S. Department of Human Health Services (HHS 2008), a more coordinated approach for effectively translating genetic and genomic applications into clinical practice and health policy is needed.

Physicians play a central role in the implementation of testing and referral, but many do not have a strong background in either genetics or pharmacogenomics. According to the National Institutes of Health, there are clinical tests available for more than 1,300 diseases, with several hundred more under research (NIH 2010). These tests are available to the public through physicians, genetic counselors, and laboratories. The SACGHS has suggested (HHS 2008) that a large number of physicians and other health care professionals do not have the training and expertise to facilitate and interpret genetic tests.

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The committee, along with many physicians, also raised questions concerning the validity and usefulness of some of the tests. Given a strong public interest in genetic and diagnostic testing, pressure from companies selling the tests, and both physicians and patients on the receiving end of direct-to-consumer marketing for the different testing systems, it is vitally important that physicians and other health care professionals take the time to understand the intricacies of both genetic and diagnostic tests (Sorrel 2008).

As with any health technology, evidence-based reviews can aid in clinical decision-making by improving predictability. A number of issues can interfere with the ability to effectively evaluate genetic evidence:

- Many genetic disorders are rare and the clinical data are limited
- It is not always clear what actions should be taken, based on test results, and the outcomes of interest are sometimes poorly defined
- The number and quality of studies are limited, especially randomized controlled trials that evaluate test-based interventions and patient outcomes. They may not be able to answer two important questions: Does the test have any impact on medical treatment? Does it improve outcomes?

Some genetic tests are being marketed on the basis of descriptive evidence and pathophysiology, while others are advocated by the industry without being fully validated (Teutsch 2008).

The ACCE model. The Centers for Disease Control and Prevention (CDC) National Office of Public Health Genomics (NOPHG) established the Analytic validity, Clinical validity, Clinical utility, and Ethical, legal, and social implications framework, or ACCE model (Figure), as a process for evaluating scientific data on emerging genetic tests (CDC 2010a).

The EGAPP initiative. Launched by the CDC in 2004, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative builds on the ACCE model structure and experience (CDC 2010b). Its purpose is to establish a systematic evidence-based process for assessing genetic tests and other applications of genomic technologies in clinical and public health practice and to develop recommendations based on that evidence. The CDC will also integrate recommendations from professional organizations. These recommendations will subsequently allow health care providers, consumers, and payers make safe and useful testing decisions.

TEST APPLICATIONS

Genetic tests are heterogenous and evaluate for diverse data; therefore, it is necessary to categorize the various tests, especially in the wake of numerous assays now in development or entering the marketplace. One method is through the test application itself, which can be divided into several different categories such as carrier screening tests, diagnostic tests, applications that show disease risk or susceptibility, and tests that show prognosis. There are also pharmacogenomic tests that predict treatment response or adverse events. Tests also can be categorized by disease or a specific condition, such as breast and colorectal cancer, or by a test's specific technology, which may include gene expression profiling.

Selected sources for technology assessments

- Evaluation of Genomic Applications in Practice and Prevention (EGAPP)
- BlueCross BlueShield Association Technology Evaluation Center
- California Technology Assessment Forum
- Agency for Healthcare Research and Quality
- U.S. Preventive Services Task Force
- ECRI Institute (formerly the Emergency Care Research Institute)
- Hayes, Inc.

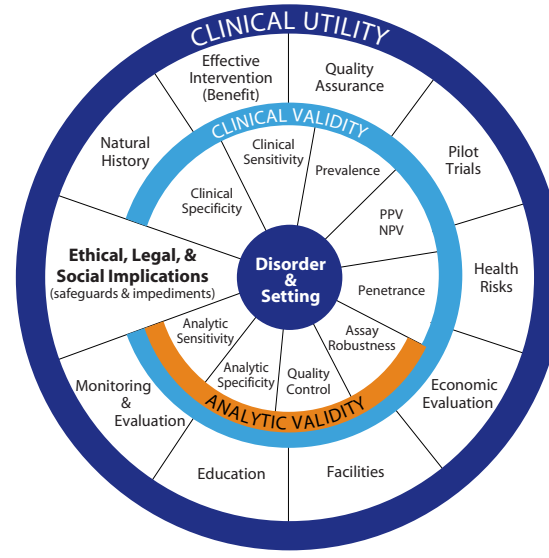
Source: Author analysis

ECONOMIC ANALYSES ARE ESSENTIAL

A sufficient amount of clinical data is needed to validate tests before cost savings can be quantified. Beyond

FIGURE

The Analytic validity, Clinical validity, Clinical utility, and Ethical, legal, and social implications (ACCE) model



NPV=negative predictive value; PPV=positive predictive value
Source: CDC 2000a

clinical issues, a key barrier to the adoption of technologies is the personalized medicine economic value proposition for public and private payers. Payers are key stakeholders, and they need to know if the high costs of diagnostics are sustainable and if many individuals need to be tested in order to identify the few who may derive a benefit from this technology. Although cost-effectiveness analyses of genetic tests are limited in the published scientific literature, real-world data are beginning to emerge from a number of areas and include data from claims systems and novel collaborations among payers, academic institutions, and laboratories.

Economic analyses to evaluate the cost-effectiveness of genetic testing are needed, because personalized medicine, or the therapeutic use of genetic tests and molecular diagnostics, is fast becoming one of the growth segments of medical spending. According to an analysis conducted by PricewaterhouseCoopers (PWC 2009), the total market for personalized medicine is estimated at $232 billion and is projected to increase by 11 percent annually. By this projection, total market costs will nearly double in size by 2015 to over $450 billion. The core personalized medicine market, which is primarily comprised of diagnostic tests and targeted therapies, is currently estimated at $24 billion and is expected to grow by 10 percent annually to $42 billion by 2015 (PWC 2009). These economic projections clearly suggest a significant impact on both the medical and pharmaceutical sides of the business.

Although diagnostic testing can increase medical costs, it also has the potential to decrease pharmacy costs; that is, laboratory spending may rise, but the utility of the test could decrease spending on the pharmacy side through better use of drug therapies. With more than 3,000 genetic tests available, it is imperative that payers analyze their utilization and assess cost, appropriateness, and outcomes to develop coverage strategies.

HUMANA'S EXPERIENCE

Humana analysts have looked at aggregate claims data that included ICD-9 (diagnosis) codes, CPT (procedural) codes, and J (drug) codes and developed net paid per-member per-month costs for years 2006 to 2009. The data showed a rising trend, greater than 80 percent, for all lines of business, and this highlighted the need to understand the testing industry better and to develop new strategies. The main challenge in performing such an economic analysis is the current procedural terminology (CPT) coding system. CPT codes are not specific to a particular test, and most laboratories bill for a series of these nonspecific codes. Thus, it is difficult to identify genetic/diagnostic tests through claims systems, and it is necessary to look at the aggregate claims data to make claims assumptions. For this type of retrospective claims analysis, Humana selected two tests — Onco*type* DX for breast cancer and KRAS testing for colorectal cancer — and conducted a cost avoidance analysis. Questions addressed included whether the use of these tests decreased plan or pharmacy costs, and if claims data analysis could highlight opportunities to identify other data needs.

Onco*type* DX. Humana conducted a retrospective study that matched chemotherapy claims to test results, and data were reviewed for a 2-year period. The cohort included approximately 860 patients who were categorized depending on whether or not they had received chemotherapy and their Onco*type* recurrence score. Costs for the tests were compared with the average costs of chemotherapy and supportive care. The study concluded that for low-recurrence score patients, the avoided chemotherapy and supportive care costs were greater than the total amount spent for the test and resulted in a cost savings of over $1 million. By analyzing and predicting which breast cancer patients were at low risk of recurrence, and, therefore, did not require chemotherapy, the Onco*type* DX test showed the value of genetic testing as a vehicle for saving costs.

KRAS Test. A retrospective claims review was conducted for KRAS testing in patients with metastatic colorectal cancer (mCRC). This test is performed to guide the use of the epidermal growth-factor receptor (EGFR) inhibitors cetuximab (Erbitux) and panitumumab (Vectibix). Clinical data strongly suggest that only patients with a wild-type KRAS tumor derive a benefit from these 2 treatments. The American Society of Clinical Oncology (ASCO) issued a first-ever Provisional Clinical Opinion stating that all patients with mCRC who are candidates for anti-EGFR therapy should have their tumor tested for KRAS mutations in a CLIA-accredited laboratory, and if a KRAS mutation in codon 12 or 13 is detected, then patients should not receive this therapy as part of their treatment (Allegra 2009).

At Humana, the ICD-9 codes for mCRC patients are coupled with the J codes and KRAS CPT codes. From this information, the total cost avoidance can be calculated. Through claims research, cost savings from averted treatment costs (i.e., averted cetuximab or panitumumab) based on KRAS testing can be calculated. In addition, physician prescribing patterns and KRAS testing patterns also can be determined. Physicians who may not be using the test correctly or not at all can be identified and encouraged to participate through the use of an educational campaign. Humana is still in the midst of its analysis; therefore, final results are not yet available.

CONCLUSION

Numerous advances in the fields of genetics and molecular diagnostics have occurred in the last decade and have contributed to the advent of personalized medicine. Because numerous tests are available, it is necessary for health plans to perform health technology assessments

of key genetic and genomic tests. A technology assessment is an unbiased, evidence-based, review of genetic interventions that can identify the shortcomings of a technology or highlight a technology's ability to improve healthcare. The CDC's ACCE model evaluating the analytical and clinical validity, clinical utility, and ethical/legal/social issues serves as a solid framework for evaluating genetic technologies.

In addition to performing a health technology assessment, health plans may need to look at their own utilization, costs, and trends of genetic and diagnostic tests to determine their appropriateness and to develop strategies to curb inappropriate use while educating providers and members of their clinical utility. For clinically validated tests, a retrospective claims analysis of tests such as Onco*type* DX and KRAS can demonstrate value to a health plan by determining the total cost avoidance by averting unnecessary treatment costs.

Disclosure: Cari Bruins, PharmD, has no real or apparent conflict of interest with respect to companies, organizations, or proprietary products mentioned in this article.

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Incorporating Genomic Testing into Oncology Treatment Pathways

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The cost trend for oncology treatments has increased faster than for any other therapeutic area, and there is greater treatment variability than in any other medical specialty. At CareFirst BlueCross BlueShield, which serves 3.4 million members in Maryland, the District of Columbia, and Northern Virginia, oncology costs account for approximately 7 percent of all medication costs generated by the prescription benefit and major medical medications. Looking specifically at major medical medications, commonly billed by J-codes, oncology drugs are responsible for approximately 45 percent of those costs. A review of cost trends shows that while overall medical costs are increasing at a rate in the "teens," oncology costs are rising by about 25 percent to 30 percent each year. Variability in cancer treatment, due to the nature of the disease, is a major cost driver, as there are often multiple treatment regimens for any given cancer type. Treatment variability is the result of the use of new technologies, new drug and drug combination therapies, and changing treatment philosophies.

Clearly, to successfully rein in costs, the traditional model for managing oncology, such as changing the fee schedule, must be revised. What is needed is a paradigm shift from a revenue-based model, focused on drug therapy, to a pay-for-quality model, focused on evidence-based medicine.

PAY-FOR-QUALITY

CareFirst took a novel approach and created an oncology Pay-For-Quality program that is administered by P4 Healthcare Oncology (2010), an online health care service that provides comprehensive, customized strategies to increase treatment efficiency and to improve patient care. CareFirst put together a physician steering committee, composed of members of its oncology network and community and academic physicians, that was charged with looking at the available cancer treatment therapies and clinical guidelines, such as the National Comprehensive Cancer Network (NCCN) guidelines for breast and colon cancer (NCCN 2010a, 2010b), to create treatment pathways for each stage of breast, colon, and lung cancers, which would conceivably cover 85 percent to 90 percent of the population in terms of treated patients. Supportive care pathways also were created for those cancers. Oncologists and other physicians treating cancer patients were then asked to comply with these pathways. By not setting the compliance threshold at 100 percent, outliers and patients in various clinical situations could be taken into consideration. The lower percentage also allowed physicians to practice individualized medicine while being guided by an established treatment pathway.

From lessons learned in its other pay-for-performance programs, specifically in primary care, CareFirst found that by providing an efficient means to collect data and measure pathway compliance, physicians would "buy in." If a physician group meets the compliance threshold, it becomes a win-win scenario, because CareFirst is providing an incentive — a portion of the savings that is generated when treatment pathways are followed — and costs are cut by reducing the variability in patient management and improving outcomes. Although numerous barriers have made oncology management difficult from a health plan perspective, CareFirst has shown that clinical pathways work and, importantly, managed care organizations and the oncology provider community can work together.

In this article, I focus on CareFirst's treatment pathways for breast and colon cancer. Since CareFirst's innovative program became active in August 2008, compliance has been measured for the breast and colon cancers. Thus far, it appears to be a true pay-for-quality program in that physicians have not been ad-

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versely affected from a reimbursement standpoint. If physicians choose not to participate in the program, or they do not meet compliance thresholds, they are still paid in accordance with the standard fee schedule. If they do participate in the program and meet compliance thresholds, they are paid according to the standard fee schedule plus a differential.

MOLECULAR DIAGNOSTICS AND BREAST CANCER

Molecular diagnosics, such as the MammaPrint and Onco*type* DX assays, represent an advancement in the ability to predict the outcome of treatment of breast cancer with chemotherapy (Kim 2010). In 2007, the BlueCross BlueShield Association (BCBS) recognized the value of molecular diagnostic testing in the prognosis and treatment of early-stage breast cancer as a tool to better predict which patients would benefit from adjuvant chemotherapy and also recognized that an increasing number of oncologists were using gene testing, believing that there was sufficient consistency and validation for these tests to be part of their treatment plan. BCBS subsequently incorporated genetic testing in their technology assessments (BCBS 2010a), and in 2008, the NCCN included gene assays for breast cancer in its guidelines (NCCN 2010a).

In the first year of CareFirst's Pay-For-Quality program, August 2008 through July 2009, the Onco*type* DX assay was highly recommended for inclusion in the treatment pathway for women with early-stage breast cancer. In the second year of the program, the assay was a required consideration for all patients with early-stage breast cancer.

Onco*type* DX is a 21-gene expression assay that predicts chemotherapy benefit as well as disease recurrence in women with early-stage breast cancer (Paik 2004). The assay reports a recurrence score to classify patients into the following categories: Low risk (recurrence score, less than 18), intermediate risk (recurrence score, 18 to 31), and high risk (recurrence score, 31 or higher). Patients with a low-risk score are predicted to derive little benefit from adjuvant chemotherapy; those with high-risk scores, about 25 percent of the population, should be receiving chemotherapy as part of managing their disease due to the likelihood of distant recurrence within 10 years. The intermediate score, however, remains a gray area (Paik 2004).

Business Rationale. Prior to starting its program in August 2008, CareFirst analyzed the cost of treatment for its adjuvant breast cancer patients, which on average was $16,000 per patient for chemotherapy and supportive care. The question then was whether the Onco*type* DX test, which carries a list price of $3,975, would actually save money, as it would eliminate unnecessary and costly drug therapy for a potentially large number of patients.

In the two years before CareFirst's Pay-For-Quality program was initiated, 206 Onco*type* DX tests were conducted; during the first year of the initiative, there were 364 tests reported under the pathway model. Using the test list price for evaluation, it was calculated that the total cost of the Onco*type* DX test came to $1.4 million during the first year of the program (Table 1). Actual cost avoidance was considered next. Of the 364 women tested, 182 scored in the low-risk category, 125 were intermediate-risk, and 57 were high-risk. Just six patients in the low-risk category received chemotherapy. Using the average cost of $16,000 in drug costs for each of 176 patients, it was determined that a $2.8 million savings was achieved, yielding a return on investment (ROI) of almost 2:1 (Table 1). Calculating further, if 100 percent of the low-risk patients had not received chemotherapy, along with 50 percent of the intermediate patients, then the ROI would be close to 3:1. CareFirst concluded that from a health plan perspective, use of the Onco*type* DX assay substantially reduced costs.

MOLECULAR DIAGNOSTICS AND COLON CANCER

Mutated KRAS genes are detected in about 40 percent of metastatic colorectal cancer (mCRC) patients, depending on the testing method used, and it has been established that these mutations can affect tumor response to the epidermal growth-factor receptor (EGFR) inhibitors. Cetuximab (Erbitux) and panitumumab (Vectibix) have been approved for the treatment of mCRC, usually as second- or third-line treatment.

In 2009, the NCCN updated its guidelines for colon and rectal cancers (NCCN 2010b). The American Society of Clinical Oncology then released a provisional clinical opinion recommending that all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy have their tumor tested for KRAS mutations in a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory, and if KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-

TABLE 1
CareFirst's Onco*type* DX assay business rationale

	Prior to 7/31/08	*8/1/08 – 7/31/09*
Total tests completed	206	364
List cost of test ($3,975)	$818,850.00	$1,446,900.00
Actual cost avoidance	$1,465,088.40	$2,865,061.75
ROI	1:1.79	1:1.98
Potential cost avoidance	$1,595,356.48	$2,962,796.82

ROI=return on investment
Source: CareFirst BlueCross BlueShield

EGFR monoclonal antibody therapy as part of their treatment (Allegra 2009). The BlueCross BlueShield Association Technology Evaluation Center has also determined that KRAS testing is medically necessary for all patients who are candidates for anti-EGFR therapy (BSBC 2010b). As part of CareFirst's metastatic colon pathway, KRAS testing is required for all cases in which cetuximab or panitumumab might be used, and only patients with a wild-type KRAS tumor will receive these agents.

PCR-based KRAS testing vs. Target GI Polymerase chain reaction (PCR)-based KRAS testing can be done by most pathology laboratories. The Target GI test (Caris Life Sciences) employs the Sanger sequencing process. Sanger sequencing has greater specificity and is considered the "gold standard." It can be used to test for oncogenic BRAF gene mutations, which can help identify patients with metastatic disease who will benefit from anti-EGFR therapies. Table 2 shows the difference between the Target GI test and PRC-based KRAS testing for colon cancer.

When tested by the PCR-based KRAS assay, an average of 40 percent of patients will have mutations. With Target GI testing, an additional 10 percent will show a BRAF mutation, and another 20 percent will demonstrate a loss of phosphase and tensin homolog (PTEN). Evaluating PTEN status could save on costs related to inappropriate anti-EGFR therapy. Overall, about 70 percent of patients with mCRC may not be suitable candidates for anti-EGFR therapy. Additional testing beyond KRAS allows for an extra 30 percent of patients to be screened for appropriate therapy.

TABLE 2
Target GI test vs. KRAS testing for colon cancer

Target GI Test (Sanger Sequencing)	PCR-based KRAS Testing
Identifies all 14 known KRAS mutations, which can help identify additional patients where anti-EGFR treatment would not be appropriate	Identifies only the 7 most common activating KRAS mutations
Identifies less common BRAF mutations	Identifies only the most common BRAF mutations
Measures PTEN levels, which can influence anti-EGFR therapy. Approximately 15 percent to 25 percent of patients with colon cancer have inadequate PTEN levels.	Does not measure PTEN levels

EGFR=epidermal growth-factor receptor; PCR=polymerase chain reaction; PTEN=phosphase and tensin homolog
Source: Caris Life Sciences

Cost analysis of KRAS testing. EGFR inhibitors range from about $14,000 to $20,000 per patient. Traditional KRAS testing costs about $450 per assay. A model of 1,000 patients at the 40 percent rate of nonresponse to anti-EGFR inhibitors is shown in Table 3. With traditional KRAS testing, the ROI is 1:18 (ratio of cost savings to cost of test). With the higher-priced Target GI assay, 70 percent of patients are identified as nonresponders to treatment. Although, actual cost savings are nearly doubled with the Target GI test compared with the traditional KRAS test, the ROI is much lower ($5.30 vs. $18 savings for each dollar spent) due to the higher cost for the Target GI test. Nevertheless, CareFirst believes this test is the "right thing to do," because a higher percentage of the population will avoid therapy that may not be appropriate, thereby avoiding possible complications and toxicity; outcomes will be improved; and costs will be contained.

TABLE 3
KRAS vs. Target GI testing for mCRC

KRAS Test Parameter	Average Cost	Total Cost
Cost for 1,000 patients	$450	$450,000
Average cost of Erbitux per patient	$20,370	$20,370,000
40 percent nonresponse rate		$8,148,000
Projected effective Erbitux cost		$12, 222,000
Projected ROI		1:18
Target GI Test Parameter	**Average Cost**	**Total Cost**
Cost for 1,000 patients	$2,700	$2,700,000
Average cost of Erbitux per patient	$20,370	$20, 370,000
70 percent nonresponse rate		$14,259,000
Projected effective Erbitux cost		$6,111,000
Projected ROI		1:5.3

mCRC=metastatic colon cancer; ROI=return on investment
Source: Caris Life Sciences

CONCLUSION

CareFirst's Pay-For-Quality oncology program provides comprehensive, cus-

tomized strategies to increase treatment efficiency and improve patient outcomes. This program includes treatment pathways for each stage of breast and colon cancers, which conceivably can cover 85 percent to 90 percent of treated patients and has been accepted by the medical and payer communities. Importantly, it shows that payer and provider collaboration can lead to less treatment variability, which improves patient outcomes and is instrumental in reining in oncology costs.

Molecular diagnostic assays for early-stage breast cancer, such as MammaPrint and Onco*type* DX, represent an advancement in oncologists' ability to predict the outcome of treatment with chemotherapy. KRAS testing can optimize therapy for patients with mCRC who are being treated with the EGFR inhibitors cetuximab or panitumumab. Although the PRC-based KRAS test is useful in predicting the clinical benefit of anti-EGFR drugs, the Target GI test for colon cancer provides additional screening opportunities and further identifies patients whose clinical outcome will not improve with EGFR treatment.

Disclosure: Winston Wong, PharmD, has no real or apparent conflict of interest with respect to companies, organizations, or proprietary products mentioned in this article.

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CONTINUING EDUCATION POST-TEST

The Impact of Molecular Diagnostics on Treatment Pathways, Outcomes, and Cost

Please tear out the assessment/evaluation form on page 21. On the answer sheet, place an X through the box of the letter corresponding to the correct response for each question. There is only ONE correct answer to each question.

1. **Genetic and genomic tests are laboratory-developed tests that are reviewed and approved by the U. S. Food and Drug Administration.**
   a. True
   b. False

2. **Genomic tests are categorized by:**
   a. disease or specific condition
   b. pharmacogenomic tests that predict treatment response or adverse effects
   c. gene expression profiling
   d. a and c
   e. all of the above

3. **Which of the following treatment regimens is considered a standard of care for nearly all women with node-negative hormone receptor positive breast cancer?**
   a. Adjuvant chemotherapy
   b. Radiation therapy
   c. Hormone therapy
   d. Targeted therapies

4. **Gene-expression profiling by reverse transcription polymerase chain reaction (PCR) and DNA microarrays may provide better prognostic information for which subtype of breast cancer patients?**
   a. normal-like
   b. estrogen-receptor (ER)-positive (luminal-like)
   c. HER2-positive
   d. ER-negative (basal-like)
   e. triple-negative breast cancer

5. **Which of the following prognostic gene assays to determine risk of recurrence in early-stage breast cancer are now commercially available?**
   a. MammaPrint
   b. PAM50 assay
   c. Onco*type* DX
   d. a and c
   e. b and c

6. **The most useful approach to assessing patients with early-stage colon cancer might be to combine T-stage, MSI/MMR status, and well-validated gene expression assays that use a recurrence score.**
   a. True
   b. False

7. **Which of the following gene assays represent an advancement in the ability to predict the outcome of chemotherapy treatment in colon cancer?**
   a. Onco*type* DX assay
   b. KRAS test
   c. Target GI test
   d. All of the above
   e. None of the above

8. **The mutated KRAS genes have been detected in what percentage of metastatic colorectal cancer patients?**
   a. 5 percent
   b. 35 percent
   c. 10 percent
   d. 40 percent

9. **Which of the following statements is true?**
   a. Genomic tests are homogenous and evaluate for similar data.
   b. There is currently an abundance of evidence-based standards for genomic technologies.
   c. Genomic tests can help save on health care costs.
   d. The cost of genomic testing and the quantity of tests ordered have decreased in the last few years.

10. **Which of the following are viewed as barriers to the implementation of genomic testing?**
    a. Genomic tests are highly inaccurate.
    b. There are no evidence-based standards for genomic testing.
    c. Health care providers lack sufficient knowledge of genomic testing protocols.
    d. b and c
    e. a and b

CONTINUING EDUCATION ASSESSMENT/EVALUATION and CERTIFICATE REQUEST

The Impact of Molecular Diagnostics on Treatment Pathways, Outcomes, and Cost

CE Credit for Physicians and Pharmacists

I certify that I have completed this educational activity and post-test and claim *(please check one)*:

☐ Physician credit hours
☐ Pharmacist contact hours

Signature: _____

PLEASE PRINT CLEARLY

First name/MI _____

Last name _____

Degree/Specialty _____

Title _____

Affiliation _____

Mail Address _____

City _____

State _____ ZIP _____

Telephone (____) _____

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Physicians: This educational activity is approved for 1.5 *AMA PRA Category 1 credits*™.

To receive a statement of AMA PRA credit, complete this assessment/evaluation form and mail or fax it to:

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To receive a statement of ACPE credit, complete this assessment/evaluation form and mail or fax it to:

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College of Pharmacy
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Tucson, AZ 85721-0202
Fax: (520) 626-2023

Please allow 6 weeks for processing.

Release Date: Oct. 15, 2010 for a period of 2 years
Expiration Date: Oct. 15, 2012

EXAMINATION: Place an X in the box of the letter that represents the best answer to the question on page 20. There is only ONE correct answer per question. Place all answers on this form.

	A.	B.	C.	D.	E.
1.	☐	☐			
2.	☐	☐	☐	☐	☐
3.	☐	☐	☐	☐	
4.	☐	☐	☐	☐	☐
5.	☐	☐	☐	☐	☐
6.	☐	☐			
7.	☐	☐	☐	☐	☐
8.	☐	☐	☐	☐	
9.	☐	☐	☐	☐	
10.	☐	☐	☐	☐	☐

PROGRAM EVALUATION: So that we may assess the value of this self-study program, we ask that you please fill out this form.

Have the objectives for the activity been met?

1. Review the epidemiology of breast and colon cancer as well as clinical advances in treatment options and diagnostic testing for optimal care. ☐ Yes ☐ No

2. Determine the economic impact of molecular diagnostics in the identification of early-stage breast and colon cancer, allowing individualized treatment options. ☐ Yes ☐ No

3. Assess best practices in health plan oncology management programs utilizing molecular diagnostics with respect to individualizing treatment decisions, outcomes, quality of care, and cost. ☐ Yes ☐ No

4. Are there barriers that could block implementation of the new learned behaviors, strategies, or skills taught in this educational activity? ☐ Yes ☐ No

If yes, please explain

_____
_____
_____
_____

5.Was this publication fair, balanced, and free of commercial bias? ☐ Yes ☐ No

If no, please explain: _____
_____
_____
_____

Please use the following scale to answer the next three questions:

Strongly Agree..... 5
Agree.....4
Neutral.....3
Disagree.....2
Strongly Disagree.....1

Did this educational activity meet my needs, contribute to my personal effectiveness, and improve my ability to:

Treat/manage patients?
5 4 3 2 1 N/A

Communicate with patients?
5 4 3 2 1 N/A

Manage my practice?
5 4 3 2 1 N/A

Other
5 4 3 2 1 N/A

What other topics would you like to see addressed: _____
_____
_____
_____

General Comments: _____
_____
_____
_____

This activity is jointly sponsored by The University of Arizona College of Pharmacy and The University of Arizona College of Medicine at the Arizona Health Sciences Center and is provided at no cost to the participant through an educational grant from Genomic Health.