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Cost-Effectiveness of Gene-Expression Profiling for Tumor-Site Origin

John Hornberger, MD, MS[1,2,*], *Irina Degtiar, BS, BA*[1], *Hialy Gutierrez, BS*[1], *Ashwini Shewade, MS, MSc*[1], *W. David Henner, PhD, MD*[3], *Shawn Becker, MD*[3], *Gauri Varadachary, MD*[4], *Stephen Raab, MD*[5,6]

[1]*Cedar Associates LLC, Menlo Park, CA, USA;* [2]*School of Medicine, Stanford University, Stanford, CA, USA;* [3]*Pathwork Diagnostics, Inc., Redwood City, CA, USA;* [4]*University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [5]*Department of Laboratory Medicine, Memorial University of Newfoundland/Eastern Health Authority, St. John's, NL, Canada;* [6]*Department of Pathology, University of Washington, Seattle, WA, USA*

ABSTRACT

Objectives: Gene-expression profiling (GEP) reliably supplements traditional clinicopathological information on the tissue of origin (TOO) in metastatic or poorly differentiated cancer. A cost-effectiveness analysis of GEP TOO testing versus usual care was conducted from a US third-party payer perspective. **Methods:** Data on recommendation changes for chemotherapy, surgery, radiation therapy, blood tests, imaging investigations, and hospice care were obtained from a retrospective, observational study of patients whose physicians received GEP TOO test results. The effects of chemotherapy recommendation changes on survival were based on the results of trials cited in National Comprehensive Cancer Network and UpToDate guidelines. Drug and administration costs were based on average doses reported in National Comprehensive Cancer Network guidelines. Other unit costs came from Centers for Medicare & Medicaid Services fee schedules. Quality-of-life weights were obtained from literature. Bootstrap analysis estimated sample variability; probabilistic sensitivity analysis addressed parameter uncertainty. **Results:** Chemotherapy regimen recommendations consistent with guidelines for final tumor-site diagnoses increased significantly from 42% to 65% (net difference 23%; $P < 0.001$). Projected overall survival increased from 15.9 to 19.5 months (mean difference 3.6 months; two-sided 95% confidence interval [CI] 3.2–3.9). The average increase in quality-adjusted life-months was 2.7 months (95% CI 1.5–4.3), and average third-party payer costs per patient increased by $10,360 (95% CI $2,982–$19,192). The cost per quality-adjusted life-year gained was $46,858 (95% CI $13,351–$104,269). **Conclusions:** GEP TOO testing significantly altered clinical practice patterns and is projected to increase overall survival, quality-adjusted life-years, and costs, resulting in an expected cost per quality-adjusted life-year of less than $50,000.

Keywords: cancer, cost-effectiveness, diagnostic, gene expression, oncology, pathology, microarray, unknown primary.

Introduction

More than 30,000 cases of cancer of unknown primary (CUP) are diagnosed annually in the United States, representing 2% of all new cancer cases [1,2]. In other cases, a leading diagnosis for the primary site has been made; however, substantial uncertainty about the tissue-site diagnosis still remains, especially when the cancer is metastatic, poorly differentiated, or undifferentiated. This can result in an exhaustive and costly "diagnostic odyssey" [3,4].

Current National Comprehensive Cancer Network (NCCN) guideline–recommended regimens for CUP consist of paclitaxel and carboplatin with or without etoposide, docetaxel and carboplatin, gemcitabine and cisplatin, or gemcitabine and docetaxel; median survival with these treatments is 6 to 9 months [5,6]. Studies have shown that survival may be improved if cancer-specific therapy is targeted to the correct tumor type, demonstrating the need for effective and accurate identification of the tissue of origin (TOO) [5,7,8].

The NCCN guideline–recommended evaluation of metastatic or poorly differentiated CUP includes a thorough history and physical examination (including breast, genitourinary, pelvic, and rectal examinations where appropriate), complete blood cell count, urinalysis, basic serum chemistries, chest radiograph, and computed tomography or magnetic resonance imaging of the abdomen and pelvis [5]. Immunohistochemistry (IHC) testing of the biopsy material is commonly used to characterize cellular differentiation and pathological diagnosis in poorly differentiated carcinomas [5]. Studies have recognized limitations—for example, with respect to consistency, reproducibility, sensitivity, specificity, and result interpretation or reporting—of conventional morphological evaluation and IHC testing, prompting a search for more reliable and accurate methods of identifying the primary site in poorly differentiated carcinomas [9–12].

The gene-expression profiling (GEP) TOO Test (Pathwork Diagnostics, Inc., Redwood City, CA) of biopsy material has been cleared by the US Food and Drug Administration and validated to provide independent information on the TOO [13–16]. The processing laboratory has Clinical Laboratory Improvement Amendments certification. The GEP TOO test is a microarray, reagent, and analytics kit that uses a 2000-gene profile to quantify the similarity of tumor specimens to 15 cancer types representing 58 morphologies. GEP TOO test results provide similarity scores that

[*] *Address correspondence to:* John Hornberger, Cedar Associates, 3715 Haven Avenue, Suite 100, Menlo Park, CA 94025, USA.
E-mail: ujch@stanford.edu.

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range from 0 to 100 and indicate the most likely primary site from among a panel of 15 tissue types. The probability of obtaining a true positive tissue call with a similarity score of 30 or more is 92.9% (95% confidence interval [CI] 90.3–95.0), and the probability of obtaining a true negative tissue call with a similarity score of 5 or less is 99.7% (95% CI 99.6–99.8) [16]. In a clinical verification study, Dumur et al. [17] showed higher performance of the GEP TOO test to identify the correct tissue site compared with well-established immunohistochemical algorithms. In a subsequent clinical-utility study of 107 patients with CUP, physicians changed the primary tissue-site diagnosis in 50% of the patients (95% CI 43–58) and changed cancer-specific management in 65% of the patients (95% CI 58–73) [18].

Although the long-term clinical and economic implications of GEP TOO testing are yet to be assessed, several studies have shown that adherence to guideline-recommended treatment may result in more cost-effective management of patients with cancer [19–21]. The specific aim of our study was to assess the cost-effectiveness of GEP TOO testing in the context of the current diagnostic paradigm and standard treatment regimens.

Methods

Analytical Framework

We performed a cost-effectiveness analysis from a US third-party payer perspective to assess the effect of GEP TOO testing on quality-adjusted life-years (QALYs) and direct medical costs
over a patient's lifetime. We performed the analysis with an individual-sampling method by using data from a retrospective, observational study of patients whose physician had received the GEP TOO test results to help diagnose the tissue site of a patient's malignancy and guide appropriate therapy. The study included 107 patients whose physicians ordered and received a GEP TOO test result between July 2009 and December 2009. Patients were 18 years or older and had metastatic cancer in which the primary origin remained uncertain despite extensive clinical and pathological evaluation. The study documented changes in tumor-site diagnosis and cancer management recommendations before and after physicians received the GEP TOO test results. An institutional review board approved all aspects of the study (Quorum Review, Inc., Seattle, WA).

We defined usual care as cancer management decisions based on history and physical examination, imaging studies, selected blood tests, and pathology, including IHC (Fig. 1). With usual care, the physician selected a treatment without the benefit of diagnostic information from the GEP TOO test.

Before and after receiving the GEP TOO test results, some physicians in the study recommended a chemotherapy regimen. We refer to chemotherapy regimens that included one or more agents recommended by clinical guidelines as guideline-consistent regimens (GCRs). We refer to regimens containing no agents recommended by clinical guidelines as non-GCRs. Two independent researchers determined whether to classify each chemotherapy regimen as a GCR or non-GCR on the basis of the regimens recommended in NCCN and UpToDate guidelines for metastatic and/or poorly differentiated cancers, and according to the physician's final tissue-site diagnosis [5,22]. The two independent researchers reached the same conclusions about whether regimens were GCRs or non-GCRs for 207 of the 214 chemotherapy regimens recommended in this study; consensus was reached on 213 total cases. The uncertain regimen was a pre-GEP TOO treatment recommendation for gemcitabine and docetaxel in a patient with an initial diagnosis of CUP. After GEP TOO testing, the patient's diagnosis changed to soft tissue sarcoma and the chemotherapy treatment recommendation changed to doxorubicin and cisplatin. A third independent rater determined that the pre-GEP TOO chemotherapy recommendation was a GCR for soft tissue sarcoma and reviewed and confirmed the other six classifications on which the two other independent raters had initially disagreed.

We calculated the incremental cost per QALY gained as the ratio of the difference in lifetime costs of care and QALYs gained when physicians determined the final tissue-site diagnosis after obtaining GEP TOO test results versus before obtaining results, that is, "usual care" [23]. We computed QALYs as the product of quality-of-life (QOL) weights and literature-derived survival time. We report costs in 2011 US dollars. The model applied a standard annual discount rate of 3% for costs and benefits [23,24]. The time horizon equaled the patient's lifetime [23].

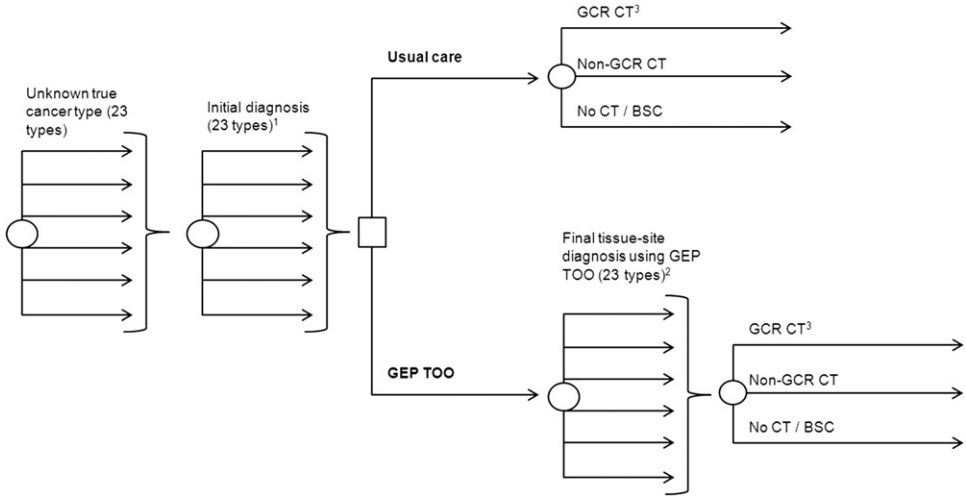

Fig. 1 – [1]Based only on history/physical examination, imaging studies, and pathology; [2]based on history/physical examination, imaging studies, pathology, and GEP TOO results; [3]whether CT is GCR versus non-GCR is based on physician's final reported tissue-site diagnosis after receiving GEP TOO results. GEP, gene-expression profiling; TOO, tissue of origin; CT, chemotherapy; GCR, guideline-consistent regimen; BSC, best-supportive care.