

## The Pathwork<sup>®</sup> Tissue of Origin Test: Clinical Need

### Overview

An estimated 200,000 newly diagnosed cancer patients annually in the U.S. may have a tumor for which the site of origin is uncertain after the initial diagnostic workup.<sup>1,2,3,4</sup> Such hard-to-identify tumors are time-consuming to work up, frustrating for both physicians and patients, and expensive to the healthcare system.

Cancers are named and treated according to their primary site. Accurately identifying the site of a tumor's origin – and thus knowing what kind of cancer the patient has – is necessary for beginning standard-of-care, cancer-specific therapy per National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines.

Identifying the site of a tumor's origin is particularly important given the emergence of new cancer-specific therapies, and can also enable patients' enrollment in potentially lifesaving clinical trials. Targeted therapies can be effective even with metastatic tumors and are generally tumor-specific (e.g., Herceptin for breast cancer), requiring identification of the primary tumor site/tissue of origin. Targeting therapy to specific tumor types can allow patients to avoid the toxicity of broader, and in some cases, useless chemotherapy.

Arriving at a diagnosis sooner can benefit cancer patients by enabling treatment to begin more quickly. Patients in whom the primary cancer is diagnosed have been shown in a prospective study to have a longer survival compared to patients in whom the tissue of origin remains unknown.<sup>5</sup>

Hard-to-identify tumors include cases in which:

- The cancer is found in an unexpected location.
- The tumor's cells are poorly differentiated or undifferentiated (i.e., they have changed appearance, making them difficult to interpret).
- The cancer is found in multiple locations, demonstrating metastatic disease without a clear primary site.

The reasons a tumor's site of origin can be hard to identify include that the original tumor may be small, eluding detection by imaging and other techniques. Additionally, the cells of the tumor in question may have changed appearance and thus may no longer resemble tumors from the originating site.

Traditional diagnostic approaches for such cases – including imaging and immunohistochemistry (IHC) – are time-consuming, require a complex iterative process and often do not produce a definitive diagnosis. Clearly, there is a need for new diagnostic methods to aid in the determination of the tissue of origin.

### Limitations of Current Diagnostic Technologies

IHC is a type of assay in which specific antigens are visualized using fluorescent dye or enzyme markers. Pathologists use various panels of IHC stains to identify the site of origin for metastatic tumors, particularly poorly differentiated or undifferentiated cancers for which morphology alone provides limited diagnostic information. IHCs have proven to be a highly useful tool to effectively rule out one or the other candidate tissues. However, choosing among three or more candidate tissues has proven to be a greater challenge, given the limited specificity and sensitivity of IHCs available. One study showed that IHC was only 67 percent accurate at identifying the primary site of metastatic tumors.<sup>5</sup> In addition, currently available IHC markers do not address the full range of potential tumor types, and the most commonly used staining phenotypes (CK7 and CK20) produce enough false positives and false negatives to make a definitive diagnosis difficult.<sup>6</sup> Thus, IHC studies alone may not provide enough information to definitively identify the primary tumor site.

Cytogenetic methods, which assess chromosomal abnormalities to pinpoint the primary tumor site, can provide insights in a number of specific situations, but generally not in a comprehensive manner. This technique is limited because only a few diagnostic chromosomal abnormalities have been identified to date.<sup>7</sup>

Imaging is also a standard tool used to assess patients with ambiguous or uncertain tumors. CT scans (particularly of the abdomen and pelvis), mammography, magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG) positron emission tomography (PET) can be helpful. These various imaging techniques may pinpoint the anatomic location of the tumor, but cannot confirm the origin of the tumor.

### **Cost Burden**

The cost to identify the primary tumor site can be significant, given that traditional approaches involve multiple diagnostic technologies that are often run in parallel. One study showed that, for certain challenging cases, the primary cancer site was found in only four (7.1 percent) of the 56 cases studied, and the average cost of diagnosis was \$17,973.<sup>8</sup> By identifying the tumor's origin, clinicians could potentially apply standard-of-care, cancer-specific therapies more quickly, potentially enabling improved patient outcomes and management of healthcare resources by reducing the use of broad-based therapies and their associated toxicities.

### **Patient Management**

When a primary site is definitively identified by either clinical or pathologic evaluation, patient management proceeds according to the NCCN Clinical Practice Guidelines for that type of cancer. Physicians increasingly have more cancer-specific treatment options. For example, 5-fluorouracil (5-FU)-based therapy was historically the treatment of choice for essentially all gastrointestinal adenocarcinoma tumors, whether they were colonic, pancreatic, or gastroesophageal in origin. However, each of these tumor types might be treated now with a more individualized approach (e.g., 5-FU/leucovorin with irinotecan or oxaliplatin for colon cancer; gemcitabine for pancreatic cancer; and epirubicin, cisplatin, and 5-FU or a taxane for gastroesophageal cancer).

The Pathwork<sup>®</sup> Tissue of Origin Test uses genomic information to enable objective, highly accurate determination of the origin of hard-to-identify tumors.

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<sup>1</sup> Pavlidis N, Fizazi K. Cancer of unknown primary (CUP). *Crit Rev Oncol Hematol*. 2005;54(3):243-250.

<sup>2</sup> Tong KB, Murtagh KN, Hubert HB, et al. Incidence, costs of care and mortality of Medicare beneficiaries diagnosed with cancer of unknown primary origin. Poster presented at the annual meeting of the American Society of Clinical Oncology; June 2-6, 2006; Atlanta, GA.

<sup>3</sup> Pathwork Diagnostics analysis.

<sup>4</sup> American Cancer Society, *Cancer Facts & Figures 2008*. Atlanta: American Cancer Society; 2008.

<sup>5</sup> Dennis JL, Hvidsten TR, Wit EC, et al. Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm. *Clin Cancer Res*. 2005;11(10):3766-3772.

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<sup>7</sup> Pavlidis N, Briasoulis E, Hainsworth J, Greco FA. Diagnostic and therapeutic management of cancer of an unknown primary. *Eur J Cancer*. 2003;39:1990-2005.

<sup>8</sup> Schapira DV, Jarrett AR. The need to consider survival, outcome, and expense when evaluating and treating patients with unknown primary carcinoma. *Arch Intern Med*. 1995;155:2050-2054.